DESIGN AND *INVITRO* EVALUATION OF GASTRORETENTIVE TABLETS OF EZETIMIBE

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University, Chennai

In partial fulfillment for the requirement of the degree of

MASTER OF PHARMACY

(Pharmaceutics)

OCTOBER- 2016

DEPARTMENT OF PHARMACEUTICS

KMCH COLLEGE OF PHARMACY

KOVAI ESTATE, KALAPATTI ROAD, COIMBATORE- 641048

DESIGN AND *INVITRO* EVALUATION OF GASTRORETENTIVE TABLETS OF EZETIMIBE

Dissertation submitted to

The Tamil Nadu Dr. M.G.R Medical University, Chennai

In partial fulfillment for the requirement of the degree of

MASTER OF PHARMACY

(Pharmaceutics)

OCTOBER-2016

Submitted by

Reg.no:261410910

DEPARTMENT OF PHARMACEUTICS

KMCH COLLEGE OF PHARMACY

KOVAI ESTATE, KALAPATTI ROAD, COIMBATORE- 641048

DR. A RAJASEKARAN, M.Pharm., Ph.D.,
PRINCIPAL,
KMCH COLLEGE OF PHARMACY,
KOVAI ESTATE, KALAPATTI ROAD,
COIMBATORE– 641048. (TN)

CERTIFICATE

This is to certify that this dissertation work entitled **"DESIGN AND *INVITRO* EVALUATION OF GASTRORETENTIVE TABLETS OF EZETIMIBE"** was carried out successfully by **Reg.no:261410910.** The work mentioned in the dissertation was carried out at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore - 641048, for the partial fulfillment for the Degree of Master of Pharmacy and is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai during the academic year **2015-2016.**

Date:
Place: Coimbatore

DR. A RAJASEKARAN, M.Pharm., Ph.D.,
Principal

GUIDE
DEPARTMENT OF PHARMACEUTICS,
KMCH COLLEGE OF PHARMACY,
KOVAI ESTATE, KALAPATTI ROAD,
COIMBATORE- 641048.

CERTIFICATE

This is to certify that the project work entitled **"DESIGN AND *INVITRO* EVALUATION *OF* GASTRORETENTIVE TABLETS OF *EZETIMIBE*"** was carried out successfully by **Reg.no:261410910.** The work mentioned in this dissertation was carried out at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore – 641048, under my guidance to The Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** during the academic year **2015-2016**.

Date: **Guide**
Place: Coimbatore

DECLARATION

I do hereby declare that this dissertation entitled "**DESIGN AND *INVITRO* EVALUATION OF GASTRORETENTIVE TABLETS OF EZETIMIBE**" submitted to the Tamil Nadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** was done at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year **2015-2016**.

(Reg.no:261410910)

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN AND *INVITRO* EVALUATION OF GASTRORETENTIVE TABLETS OF EZETIMIBE"** submitted by **Reg.no:261410910** to the Tamil Nadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by the candidate at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, and was evaluated by us during the academic year **2015– 2016**.

Examination Centre: KMCH College of Pharmacy, Coimbatore – 48.

Date:

Internal Examiner **External Examiner**

Convener of Examination

ACKNOWLEDGEMENT

The Almighty God, I am thankful and grateful to you for the constant support not only for my project but for all the achievements in my life. I bow down to you with both my hands folded.

Words seem to be too small for expressing my thanks to the following persons.First and foremost, I wish to express my sincere thanks and deep appreciation to my **Guide,** Professor, Department of Pharmaceutics, KMCH College of Pharmacy, for suggesting idea for this study, his infinite support, patience, follow up, close and wise guidance in my project.

I extend my sincere thanks and gratitude to our beloved Chairman **Dr.Nalla G. Palaniswami, MD, AB (USA)** and respected Managing trustee **Dr.Thavamani D. Palaniswami, MD, AB (USA),** Kovai Medical Center Research and Education Trust, Coimbatore for all the facilities that were provided to me at the institution enabling me to do the work of this magnitude.

I take a step forward to express my deep regards to **DR. A Rajasekaran, M.Pharm., Ph.D.,** Principal, KMCH College of Pharmacy, for his constant encouragement, support and facilities provided to carry out this work.

I express my deep gratitude to **DR. K S G ArulKumaran, M.Pharm, Ph.D.,** Head of Department of pharmaceutics, for his constant insight, advice and countless serenity in all stages of study.

I owe my heartfelt thanks to my esteemed and beloved staffs **DR. K T Manisenthil Kumar, M.Pharm., Ph.D., DR. K Suresh Kumar, M.Pharm., Ph.D.,** for their sensible help and suggestions.

My sincere thanks to all other staffs of KMCH College of Pharmacy, Coimbatore who directly or indirectly gave a helping hand to me while carrying out the study.

This project would not be a resplendent one without the continuous support of my best buddies **SaliKrishna SB, Aswathy Prakash , Hareesh Krishnan, Jithin, Suhad TK and Joyce Rose Thomas.**

I express my heartfelt gratitude to my dear friends **Gibi, Rekha Babu, Krithika, Kanchana, Deepthi, Sangeetha, Soundarya and Alga** for their support and assistance to carry out my project.A hearty thanks to my seniors **Winnie Rose Jacob** and **Bestin K Martin** for their support and help.

I express my gratitude to my dear roommate **Sanju Kaladharan** for her support.

I also express thanks to **Ms.Thiruveni,** Lab technician (Dept of Pharmaceutics) and **Mrs. Anandhi** (Dept. of Pharmaceutical analysis) for their valuable support and timely help during the course of the entire work..

'Thanks' is a small word for the constant love and encouragement given to me by my beloved parents **C.C Varughese** and **Anie Varughese** and my loving siblings **Anu, Joel** and **Abhay Philip**. It is with their blessings, prayers and love that I have reached till here in my life.

Thanks to all those for whom I am unable to name individually, but still remember with appreciation.

Above all I dedicate myself before the unfailing presence of **God Almighty** throughout the way of my success.

Reg.no:261410910

CONTENTS

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. This results in a significant fluctuation in drug levels. Recently several advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits.[1]

The de novo design of an oral controlled drug delivery system (DDS) must be primarily aimed to achieving more predictable and increased bioavailability of drugs.

However, the development process is precluded by several physiological difficulties, such as inability to restrain and localize the DDS within the desired regions of the GIT and the highly variable nature of the gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12hrs.

This variability may lead to unpredictable bioavailability and time to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Furthermore, due to the relatively brief gastric emptying time (GET) in humans, this normally has an average of 2-3 hrs through the major absorption zone (stomach or upper part of the intestine), it can result in incomplete drug release from the (DDS) leading to diminished efficacy of the administered dose.

Thus control of placement of a DDS in a specific region of the GIT offers numerous advantages, especially for drugs exhibiting an absorption window in the (GIT) or drugs with a stability problem. These considerations have led to the development of oral controlled – release (CR) dosing forms possessing gastric retention capabilities. [2]

After oral administration, a drug delivery system in such a manner, would be retained in the stomach and would release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the (GIT). Gastro-retentive drug delivery is an approach to prolong to residence time, thereby targeting site-specific drug release in the upper gastrointestinal (GIT) for local or systemic effects.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Stomach physiology:

Anatomically the stomach is divided into 3 regions: fundus , body and antrum(pylorus). The proximal part is made of fundus and the body acts as a reservoir for undigested material, whereas the antrus is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

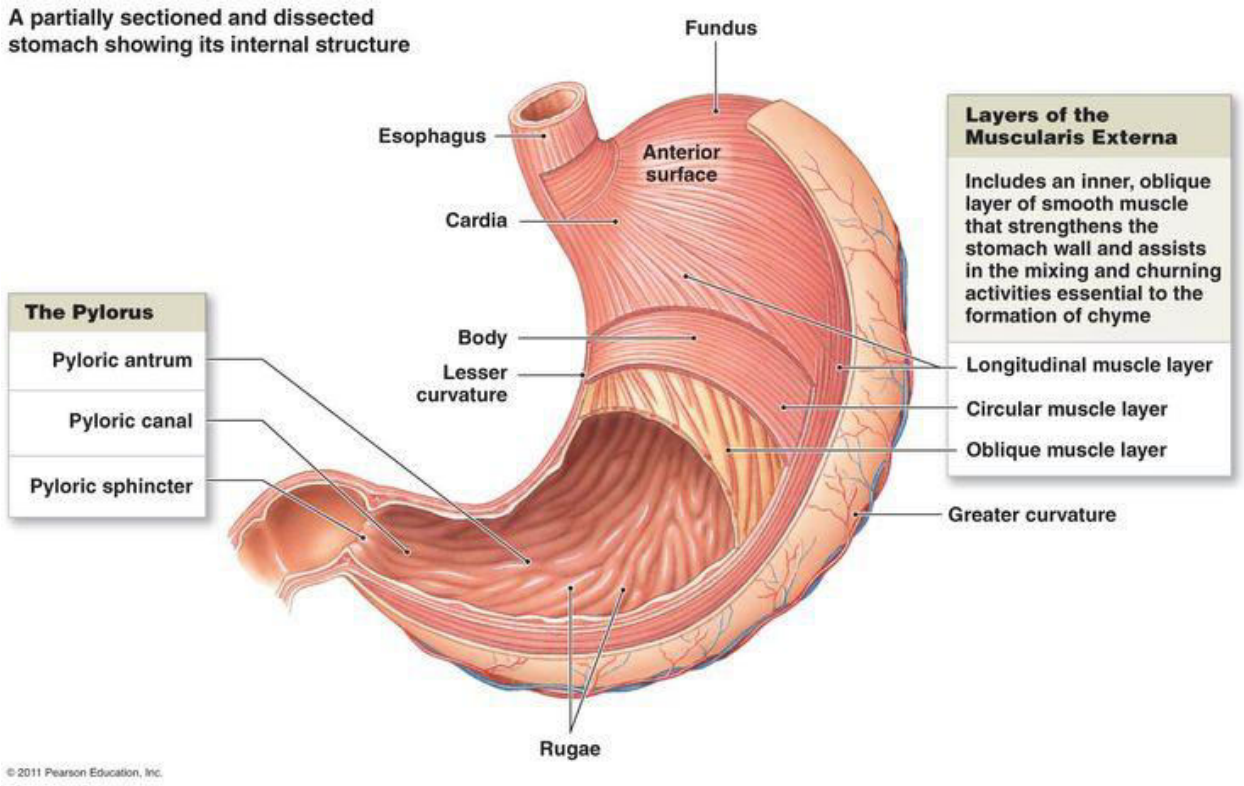


Fig 1: Physiology of Stomach

FUNCTIONS OF STOMACH[3]:

- Temporary food storage
- Controls the rate at which food
- enters the duodenum
- Acid secretion and antibacterial action
- Fluidisation of the stomach contents
- Preliminary digestion with pepsin, lipases etc

Gastric emptying[4]:

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in both the states. During the fasting state an inter digestive series of electrical event takes place, which cycle both through the stomach and intestine every 2 to 3 hours. This is called interdigestive myoelectric cycle or migrating myo electric cycle (MMC), which is further divided into following 4 phases by Wilson and Washington.

Table 1: Phases of Migrating Myoelectric Cycle (MMC)

Phases	Name	Duration	Nature
Phases 1	Basal phases	45-60min	Rare contractions
Phases 2	Pre-burst phases	30-45min	Intermittent peristaltic contraction which gradually increase in intensity frequency
Phases 3	Burst phases or "house keeper waves"	5-15min	Large intense peristaltic contraction.
Phases 4	Brief transitional phases	0-5 min	Occurs between phases 3 and phases 1 of the cycle.

After the ingestion of food, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contraction as in phases II of fasted state.

These contractions result in reducing the size of food particles (to less than 1mm), which are propelled toward the pylorus in a suspension form.

During the fed state, onset of MMC is delayed, resulting in slowdown of gastric emptying rate. Scintigraphic studies which are used to determine gastric emptying rates revealed that orally administered controlled release dosage forms are subjected that of short gastric residence time and unpredictable gastric emptying rate.

SUITABLE DRUG CANDIDATES FOR GASTORETENTION[5]:

1. Drugs that are having narrow absorption window in GIT(e.g. L-DOPA, P-aminobenzoic acid, Furosemide, Riboflavin)
2. Drugs those are locally active in the stomach(e.g. misroprostol, antacids)
3. Drugs those are unstable in the intestinal or colonic environment (e.g. Captopril, Randitine HCl, and Metronidazole)
4. Drugs that disturb normal colonic microbes(e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, Clarithromycin, Amoxcillin).
5. Drugs that exhibit low solubility at high pH values (e.g. diazepam, Chlordiazepoxide, Verapamil)

FACTORS AFFECTING GASTRIC RETENTION[6]:

The gastric retention (GRT) of dosage form is controlled by several factors, which affect their efficacy as a gastro retentive system.

- **Density**- Density of a dosage form affects the gastro retention time of the dosage form.

- **Size –**Dosage forms with a diameter of more than 9.5mm are reported to have an increased GRT.

- **Shape of dosage form –** Tetrahedron and ring-shaped device with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) were reported to have better GRT i.e 90% to 100% retention at 24 hours compared with other shapes.

- **Fed or unfed state-** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric cycle (MMC) that occurs every 1.5 to 2 hours.
  The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit is expected to be very short. However, in this state, MMC is delayed and GRT is considerably longer.

- **Nature of meal-** Feeding of indigestible polymers or fatty acid salts will change the motility pattern of the stomach to a fed state, thus decreases the gastric emptying rate and helps to prolong drug release.

- **Caloric content**- GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

- **Frequency of feed-** The GRT can increase by over 400 minutes when successive meals are given compared to a single meal due to the low frequency of MMC.

- **Gender-** Mean ambulatory GRT in males (3.4±0.6 hours) is less when compared to their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

- **Age-** Elderly people, especially those over 70, have a significantly longer GRT.

- **Posture**- GRT can vary between supine and upright ambulatory states of the patient.

- **Concomitant drug administration-** Anticholinergic drugs like Atropine and Propantheline

- **Biological factors:** Diabetes and crohn's disease.

TYPES OF GASTRORETENTIVE DOSAGE FORMS[6][7]

1) **FLOATING DRUG DELIVERY SYSTEMS**

Floating drug delivery systems (FDDS) have a bulk density less than that of gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the delivery system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This resulted in increased GRT and better control of the fluctuations in plasma drug concentration.

Floating drug delivery systems can be further divided into:

a) **Non-effervescent system**
b) **Effervescent system**

2) **EXPANDABLE SYSTEMS**

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that improve their GRT. After the drug release, their dimensions are minimized with subsequent evacuation from the stomach.

3) BIO/ MUCO-ADHESIVE SYSTEMS

Bio adhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of various bioadhesive polymers, which can adhere to the epithelial surface in the stomach.

Gastric mucoadhesion does not tend to be strong enough to impart to the dosage forms, the ability to resist the strong propulsion forces of the stomach wall. The continous production of the mucous by the gastric mucosa to replace the mucous which is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force.

Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lecithins etc.

4) HIGH-DENSITY SYSTEMS

Sedimentation has been employed as retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is part of the organ with the lowest position in a upright posture.

Dense pellets (approximately $3g/cm^3$) that are trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With the pellets, the GI transit time can be increased to an average of 5.8-25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium oxide and iron powder, etc. These materials increase density by up to $1.5\text{-}2.4g/cm^{-3}$.

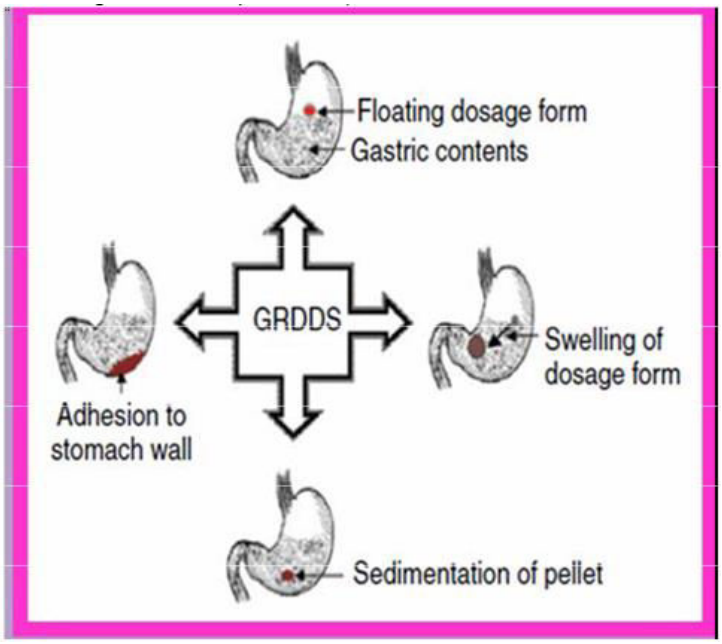


Fig 2: Types of GRDDS

FLOATING DRUG DELIVERY SYSTEM[8]

Floating drug delivery systems are also called as hydrodynamically balanced systems that float on the gastric contents to release the drug slowly from the dosage form. It is further divided into:

a) Non effervescent systems:

This type of system, after swallowing, swells unrestrained via inhibition of gastric fluid to an extent that prevents their exit from the stomach. One of the formulation methods of such dosage form involved the mixing of the drug with a gel, which swells when in contact with the gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density less than one within the outer gelatinous layer. The air trapped by the swollen polymer offers buoyancy to these dosage forms.

Excipients which are most commonly used include hydroxyl propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into four sub-types:

(i) Colloidal gel barrier system

Sheth and Tossounian first designed this 'hydrodynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach contents. This prolonged the GRT and maximized the amount of drug that reached its absorption sites in the solution form for ready absorption. This level incorporated a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g. hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyl propyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with the gastric fluid, the hydrochloride in the system hydrated and formed a colloid gel barrier around its surface.

ii) Micro-porous compartment system:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing the entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and transports the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate beads:

Multi-unit dosage forms are developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter is prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, using the precipitation of calcium alginate. The beads are then separated, snaped frozen in liquid nitrogen and freeze dried at 40^0C for 24 hours, leading to the formation of a porous system which can maintain a floating force for over 12 hours. These floating beads gave a longer residence time of more than 5.5 hours.

(iv) Hollow microspheres/ Micro balloons

Hollow microspheres which are loaded with drug in their outer polymer shelf are prepared by novel emulsion solvent diffusion method. The ethanol/ dichlormethane solution of the drug and enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) and was thermally controlled at 40^0C. The gas phase was generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and the internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously on the surface of an acidic dissolution media containing the surfactant for more than 12hrs.

b) Effervescent System

These buoyant systems utilizes matrices prepared with swellable polymers such as methocel, polysaccharides (e.g. chitosan), effervescent compound (e.g. sodium bicarbonate, citric acid, tartaric acid). The system is prepared so that upon arrival in the stomach,carbon dioxide is released, causing the system to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that evolve carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrolidine are coated with hydroxyl propyl methyl cellulose (HPMC) and floating systems based on ion exchange resin technology etc.

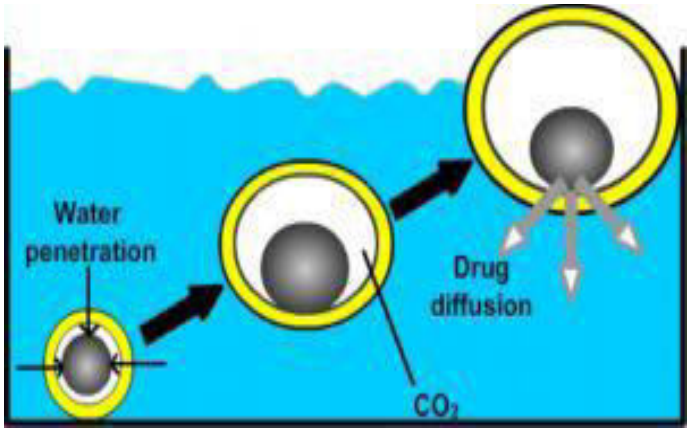


Fig 3: Effervescent system

Mechanism of Floating Drug Delivery System[9]:

Floating drug delivery systems (FDDS) have a bulk density lesser than gastric fluids, so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the formulation.

However, a minimal gastric content is needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.
To measure the floating force kinetics, a novel apparatus for determination of resultant weight was reported. The apparatus operates by measuring continuously the force equivalent to F(as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side.
This apparatus helps in optimizing FDDS with respect to the stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F_{buoyancy} - F_{gravity}$$

$$= (D_f - D_{s)}\, gv \text{------ (1)}$$

Where F= total vertical force, D_f = fluid density, D_s= object density, v=volume and g= acceleration due to gravity.

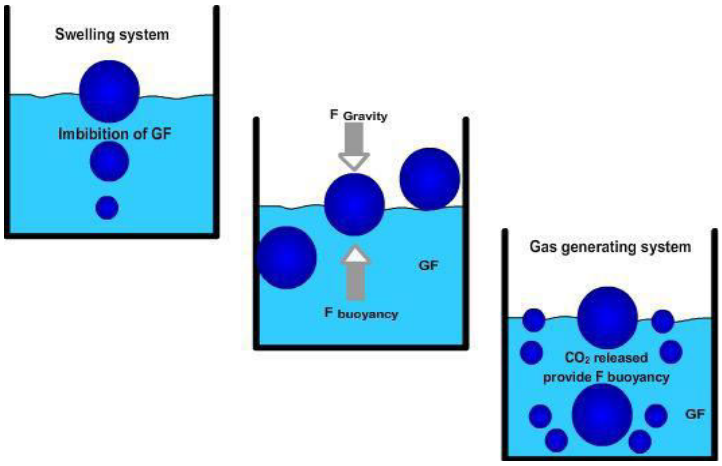


Fig 4: Mechanism of Floating Systems

The main requirements for floating drug delivery system are:

1) It must release contents slowly to serve as a reservoir.
2) It should maintain specific gravity lower than gastric contents(1.004-1.01 gm/cm^3)
3) It should form a cohesive gel barrier.

Advantages of floating drug delivery system[10]

- Improved drug absorption due to increased gastric residence time and more time spent by the dosage form at its absorption site.
- Controlled release of drugs.
- Delivery of drugs is localized in the stomach.
- Minimizes the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro-oesophageal reflex.
- Simple and convenient equipment for manufacture.
- Easy administration and better patient compliance.
- Site specific delivery.

Limitations of Floating Drug Delivery Systems:

- Must be administered with plenty of water.
- Floating systems are not feasible for those drugs which have solubility or stability problems in gastric fluids.
- Drugs such as Nifedipine, is well absorbed along the entire GI tract and undergoes significant first- pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavalibility. There are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
- Gastric retention are influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

FORMULATION OF FDDS:
Excipients Used in FDDS:

1) **Polymers:**
   The following polymers are used in the preparation of FDDS- HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL Propylene foam, Eudragit RS, ethyl cellulose, PVA, Polycarbonate, Acrylic polymer and carbopol

2) **Inert fatty materials (5%-75%)**
   Edible, inert fatty material having a specific gravity of less than one is used to decrease the hydrophilic property of formulation and hence increase buoyancy.
   E.g. Beeswax, fatty acids, long fatty acids. Gelucires 39/01.

3) **Effervescent agents:**
   Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di- Sodium Glycine Carbonate, CG (Citroglycine).

4) **Release rate accelerants (5%-60%):**
   e.g. Lactose, mannitol

5) **Release rate retardants (5-60%):**
   e.g. Dicalciumphospate, talc, magnesium stearate

6) **Buoyancy increasing agents upto 80%:**
   e.g. Ethyl cellulose

7) **Low density material:**
   Polypropylene foam powder (Accurel MP 1000)

POTENTIAL DRUG CANDIDATES FOR FLOATING DRUG DELIVERY SYSTEMS[11]:

1) **Drugs which are locally active in the stomach:** e.g.misoprostol, antacids etc.

2) **Drugs that have a narrow absorption window in gastrointestinal tract (GIT):** e.g. L-Dopa, Para amino benzoic acid, furosemide, riboflavin etc.

3) **Drugs that are unstable in the intestinal or colonic environment :** e.g. captopril, ranitidine, metronidazole.

4) **Drugs that disturb the normal colonic microbes:** e.g. antibiotics against Helicobacter pylori.

5) **Drugs those exhibit low solubility at high pH values:** e.g. diazepam, chlodiazepoxide, verapamil HCl.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS[12]:

1) **Enhanced bioavailability:**
   The bioavailability of riboflavin CR-GRDF was significantly enhanced in comparison to the administration of non-GRDFCR polymeric formulations. There are several processes, related to the absorption and transit of the drugs in the gastrointestinal tract, that act commitantly to influence the magnitude of drug absorption.

2) Sustained Drug delivery:

Oral CR formulations were encountered with problems such as gastric residence time in the GIT. These problems can be overcomed with HBS systems which can remain in the stomach for long periods and have a bulk density< 1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is barred.

3) Site specific drug delivery systems:

These systems were particularly advantageous for drugs that are specifically absorbed from the stomach or proximal part of the small intestine. The controlled, slow delivery of the drug to the stomach provides sufficient local therapeutic level and limits the systemic exposure to the drug. This reduced the side effects that are caused by the drug in the blood circulation. In addition, the increased gastric availability from a site directed delivery system may also reduce the dosing frequency. Eg. Furosemide and Riboflavin.

4) Absorption enhancement

Drugs that are having poor bioavalibility because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

5) Minimized adverse activity at the colon:

Retention of the drug in the HBS systems at the stomach minimized the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon was prevented.

GRDF formulation for betalactum antibiotics were absorbed from the small intestine, and its presence in the colon led to the development of micro organism's resistance.

6) Reduced fluctuations of drug concentration:

Continuous input of the drug following CRGRDF administration produced blood drug concentrations within a narrower ranges compared to the immediate release dosage forms. Thus, fluctuations in drug effects are reduced and concentration dependent adverse effects that are associated with peak concentration.

LITERATURE REVIEW

Kristl et al.[13] investigated the development of floating matrix tablets, which after oral administration were designed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects of the irritating drugs. The importance of the composition optimization, the technological process development for the preparation of the floating tablets with a high dose of freely soluble drug and characterization of those tablets(crushing force, floating properties in vitro and in vivo, drug release) was examined. Tablets containing hydroxypropyl methyl cellulose (HPMC), drug and different additives were compressed. The investigation shows that tablet composition and mechanical strength have the greatest influence on the floating properties and drug release. With the incorporation of a gas-generating agent together with microcrystalline cellulose, besides optimum floating(floating lag time, 30s; duration of floating, >8 hrs), the drug content was also increased. The drug release from those tablets was sufficiently sustained (more than 8hrs) and non-Fickian transport of the drug from tablets was confirmed. Radiological evidence suggests that, the formulated tablets did not adhere to the stomach mucus and that the mean gastric residence time was prolonged(>4hrs).

Srividya et al[14]. developed gastro retentive floating matrix tablets of Quetiapine fumarate by using various hydrophilic polymers. The formulation was developed by using different concentrations of polymers of various grades of HPMC and guar gum. The gas generating agent of sodium bicarbonate was optimized. The formulation blend was subjected to various preformulation studies, and all the formulationswere found to be indicating that the powder blend has good flow properties. Among all the formulations, the formulations prepared by guar gum were unable to produce desired drug release; they were unable to retard drug release upto 12hours. The formulations prepared with HPMC K15 M retarded the drug release upto 12hours in the concentration of 120 mg (F6). The formulations prepared with HPMC K100 M (F8) also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

Bhandari et al[15]. developed chronomodulated floating drug delivery system for famotidine; the formulations were evaluated and optimized for their desired effect. By using present drug delivery system, famotidine was delivered locally to the stomach with a certain period of lag time. Different levels of percentage weight ratio of ethyl cellulose to hydroxypropyl cellulose and different coating levels were successfully optimized by using statistical analysis. Combing 32 factorial design and response surface methodology % weight ratio of polymers and coating levels were optimized for desired lag time of off release and cumulative drug release. Response surface methodology represents combined effect of both independent variables on dependent

variables. So we can predict optimum levels of independent variables for desired responses. For the present study of formulating chronomodulated drug delivery system optimized coating level percentage weight gain was 7.50% and the percentage weight ratio of ethyl cellulose to hydroxypropyl methyl cellulose was 78.50% that gave observed lag time of 218 minutes and percentage cumulative drug release of 88.21% with minimum percentage error with predicted values from the software.

Ying-Chen Chen et al[16]. developed effervescent multiple-unit floating drug delivery systems to prolong the gastric residence time and to improve the overall bioavailability. These systems comprised of the drug (losartan), effervescent agent (sodium bicarbonate) containing pellets coated with a blended polymeric membrane which was a mixture of gastro intestinal soluble and insoluble polymers. The addition of GIT- soluble polymers such as HPMC, PEG 6000 increased the water uptake ability of the GIT-insoluble polymers and helped to initiate the effervescent reaction and float, but the hydrated films was impermeable to the generated CO_2 and thereby helped to maintain the floatation. It was sufficiently flexible to withstand the pressure of carbon dioxide to avoid rupturing. The study demonstrated that the water uptake ability and mechanical properties can be applied as screening tools during the development of effervescent muFDDSs. The optimized system of SRT(5) P600(5) (i.e a mixture of 5% Kollicoat SR and 5% PEG 600) with a 20% coating level started to float within 15minutes and maintained its buoyancy over a period of 12hrs with sustained release effect.

Rajani Shakya et al[17]. developed hydrophilic matrix based controlled release gastro retentive drug delivery system of ofloxacin and its *in-vitro* and *in-vivo e*valuations. Effervescent floating gastro retentive drug delivery system of ofloxacin was prepared by utilizing Box-Behnken statistical designs. Formulation was optimized by setting targets on selected responses. *In- vivo* were carried out for the optimized formulation with 12 healthy volunteers and the obtained pharmacokinetic parameters were compared with the marketed daily once formulation. Optimized formulation showed satisfactory controlled *in-vitro* drug release for more than 12hrs, having excellent buoyancy properties(floating lag time<1min, floating duration > 16hrs). The optimized and marketed formulations were found to have similar *in-vitro* release profile (f2=79.22) and were also found to be bioequivalent. C_{max} and AUC values of optimized formulation were found to be significantly higher than that of marketed formulation despite their bioequivalence.

Govikari Koteshwar Rao et al[18] designed and developed gastro retentive dosage forms for cefuroxime axetil using floating tablet approach with various grade of hydroxyl propyl methyl cellulose. Sodium bicarbonate was used in the dosage form as a source of effervescent agent to maintain buoyancy. *In vitro* dissolution study results indicated that the formulation was non-Fickian diffusion controlled release mechanism and it was best fitted into Korsmeyer-Peppas equation. *In vivo* radiographic studies was conducted in five healthy human volunteers for the optimized formulation and it indicated over 6hr retention of tablet in the stomach region.

Friederike Eisenacher et al[19] evaluated the performance of Co_2 generating floating bi layer tablets with respect to robustness, drug release profile, pH dependence and floating behaivour. Bilayer tablets were coated with a flexible and water permeable, but CO_2- retaining polymer film of polyvinyl acetate or ammonio-methacrylate copolymer type A. Metformin HCl was used as a relevant model drug due to its dose dependency and saturable absorption from the proximal part of the small intestine. To mimic the physiological relevant mechanical stress conditions, dissolution stress tests were recently developed and pulsed pressures were applied in addition to release studies according to the pharmacopoeia. Bilayer tablets coated with polyvinyl acetate showed short floating lag time, floating duration of more than 24 hrs in simulated gastric fluid and a robust and pH independent release of Metformin HCl. Tablets that are coated with ammonio- methacrylate copolymer type A showed higher permeability for the active ingredient combined with a decreased robustness of the inflated tablets. Both polymers are used for balloon like floating devices. The appropriate polymer chosen is dependent on the properties of active ingredient and the application of the delivery device was requested.

Chandrasekhara Rao Baru et al[20] developed ibuprofen floating tablets by using various polymers such as HPMC K4M and Carbopol 940 to enhance the bioavailability and therapeutic efficacy of ibuprofen. The floating tablets of ibuprofen are prepared by direct compression method. Four formulations (F1 to F4) were prepared by using variable concentrations of HPMC K4 and Carbopol 940. DSC analysis was performed to ensure there were no interactions between drug and the polymers. The optimized formulation showed satisfactory release for more than 12 hours, have shorter floating lag time increased bioavailability.

Navjot Singh et al[21] developed a gastro retentive system for tizanidine hydrochloride. Floating matrix tablets of tizanidine hydrochloride were prepared by employing hydroxyl propyl methyl cellulose as encapsulant using wet granulation technique. The precompression parameters for the floating tablets were evaluated. The drug and polymer interaction was evaluated by Fourier transform infra red spectroscopy. The gastroretentive activity of the floating tablets of THC was evaluated *in vitro* as well as *in vivo* using gamma scintigraphy technique in healthy human volunteers. The effect of polymer concentration, polymer viscosity on drug release profile was investigated. It was observed that the concentration of HPMC plays an important role in controlling the *in vitro* drug release profile of the formulations. The increase in HPMC retards the release of drug from the formulation. The *in vivo* study by gamma scintigraphic in the human volunteers by Tc 99M has shown that the floating tablet of THC can maintain its integrity under harsh conditions in the human stomach.

Mudgal Vinod Kumar et al[22] developed a sustained release floating system using ciprofloxacin as a model drug that was able to float for an extended period of time. The system consisted of a 3mm drug containing gas generating core which is formulated by direct compression and coated with a flexible polymeric membrane. Eudragit RL30D and ATEC were used as a film former and plasticizer respectively. As the proportion of effervescent agents increased, the floating time decreased. The optimized coated floating tablets floated within 20min and remained buoyant for more than 13hrs. A sustained release of ciprofloxacin for more than 13 hrs was observed. The time of floatation can be controlled by the composition (type of filler, concentration of effervescent agents) and the hardness of the tablet core and the composition (type of polymer and plasticizer) and thickness of the coating.

Ligam Meka et al[23] developed a gastro retentive floating drug delivery system with multiple-unit minitab's based on gas formation technique in order to prolong the gastric residence time and to increase the overall bioavailability of the drug. The system consisted of the drug-containing core units prepared by direct compression process, which were coated with three successive layers of an inner seal coat, effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of a polymethacrylates (Eudragit RL30D, RS30D, and combinations of them. The system which used Eudragit RL 30D and combination of them as a gas-entrapped polymeric membrane could float. The optimized formulation floated completely within 3min and maintained the buoyancy over a period of 12 hrs. The drug release was controlled and linear with the square root of time. As the coating level of gas-entrapped polymeric membrane was increased, the drug release was decreased. Both rapid floating and the controlled release properties were achieved in the multiple-unit floating drug delivery system which was developed in the present study. The analysis of the parameter dissolution data after

storage at 40^0C and 75% RH for 3 months showed no significant change hence indicating the two dissolution profiles to be similar (f2 value is more than 50).

Suraj Aghav et al[24] developed floating gastro retentive system of simvastatin to increase the gastric retention time and the bioavailability. From the findings of various physical, chemical and *in-vitro* tests, it is concluded that initially the drug was confirmed by characterization by UV spectroscopy, FT-IR spectroscopy and Differential Scanning Calorimetry. Sodium bicarbonate 15% (30mg) and citric acid 5% (10mg) imperative to achieve *in vitro* buoyancy. From the preliminary trial batches containing individual polymer, it was confirmed that 35% (70mg for 200mg tablet) of Polyvox WSR 205 and Polyvox WSR N12K was required to achieve i*n vitro* buoyancy as well as desired drug release pattern. After the dissolution profile of preliminary trial batches, it was concluded that as polymer concentration increases, drug release decreases. Formulations were prepared as per 3^2 full factorial design.

Garje Pravin et al[25] formulated a gastro retentive drug delivery system of Metoprolol tartrate. Sodium bicarbonate and citric acid were used as the effervescent agent. The effects of citric acid and sodium bicarbonate on drug release profile and floating properties were evaluated. 3^2 full factorial design was applied to systemically optimize the drug release profile. The amounts of HPMC K 15M (X1) & HPMC K100M (X2) were selected as independent variables & lag time (Y1), float time (Y2), percent drug release (Y3) were selected as dependent variables. According to the full factorial design , combination of HPMC K15M and HPMC K100M polymer favours the sustained release of metoprolol tartrate from a gastro retentive formulation. Batch F5 showed the highest drug release, (97.11%) have floating lag time of 49sec and floating time of 12hrs.

Aleksandar Aleksovski et al[26] developed controlled release effervescent matrix tablets which was meant to float over the gastric media for more than 8hrs and the active compound was released in a continous manner. Ranitidine HCl was used as a model drug which has narrow absorption window in the small intestine. Sodium bicarbonate and citric acid was employed as effervescent compounds and two different types of hydroxyl propyl methyl cellulose (HPMC K4 and HPMC K15M) were used as controlled release hydrophilic polymers.

Three batches of tablets were formulated (one containing HPMC K4, other having HPMC K15M and the third containing 1:1 mixture of these polymers). Every batch was compressed with two different forces 5.5kN and 4.7kN, hence completely six probes of tablets were made. All six probes complied to the pharmacopoeial requirements containing mass uniformity, friability and hardness.all the six probes floated fast to the surface of the medium and tended to hydrate and swell fast enough whose actions provided controlled release of the compound forover a period of 8hours. No significant differences were noticed in the dissolution profiles of all six probes during investigation.

M.A. Hassan et al[27] developed a gastro retentive drug delivery system for water-soluble H_2 – receptor antagonist drug namely ranitidine hydrochloride. The floating and controlled-release properties of tablets containing ranitidine HCl, HPMC and other additives were evaluated. The study showed that tablet composition and mechanical strength have the greatest influence on floating properties and drug release. Sodium bicarbonate was used as the gas generating agent. The time taken for the tablets to emerge on the water surface (floating lag time) or buoyant time, and the time during which the tablets constantly float on the water surface were evaluated. The results indicated that the buoyancy was strong enough for the whole tablets to travel up to the surface and remain on the surface as long as 24hrs. Drug release from the drug was sufficiently sustained and the drug release fit both Higuchi and Peppas model. The floating tablets were compared with conventional tablets in fasted rabbits at 150mg equivalent dose of ranitidine HCl. The pharmacokinetic parameters were calculated.

Dave et al[28] prepared a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthum gum and hydroxyproyl methyl cellulose were evaluated for gel-forming properties. Sodium bicarbonate was incorporated as gas generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 32 full factorial design was applied to systemically optimize the drug release profile. The amounts of citric acid anhydrous (XI) and stearic acid (X2) were selected as independent variables. The times required for 50% (t50) and 80% drug dissolution (t80), and the similarity factor f2 were selected as dependent variables. The results of the full factorial design indicated that a low amount of citric acid and a high amount of stearic acid favours sustained release of ranitidine hydrochloride from a gastroretentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride.

Ali Kadavar et al[29] developed floating sustained-release Imatinib tablets to overcome the inadequacy of conventional tablets. Tablets were formulated using HPMC K4, Sodium Alginate and Carbomer 934P as release retarding polymers, sodium bicarbonate as the effervescent agent and lactose as a filler. Floating behaivour, *in vitro* drug release, and the swelling index studies were conducted. The initial and final drug release duration was compared with a commercial tablet. Tablets were evaluated for various physical parameters including weight variation, thickness, hardness, friability and drug content. Consequently, 6 months of physical stability studies and *in vitro* gastro-retentive studies were conducted.

Pramod patel et al[30] The present study concerns the development of floating tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymer like guar gum, locust bean gum, either alone or in combination with HPMC K100 M as swelling polymers with sodium bicarbonate as gas generating agent and were evaluated for parameters such as weight variation, hardness, friability, drug content, swelling index, *in vitro* buoyancy study and *in vitro* drug release studies. All the formulation showed compliance with pharmacopeia standards. Based on the evaluation results, F3 and F6 formulations were selected as the best formulation was well controlled and uniform throughout the dissolution studies. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian / anomalous according to Korsmeyer-Peppas equation.

Thakur et al [31] developed floating matrix tablets of clarithromycin to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as for improving bioavailability. The tablets were compressed using wet granulation technique. The optimized formulation gave floating lag time less than 30 seconds and had a total floating time more than 10hours.

Prasad garrepally et. al[33] developed an intragastric drug delivery system of propanolol hydrochloride, and investigated the ability of various natural polymers to retain the drug when used in different concentrations. Mango resin i.e. *Mangifera indica* was evaluated for their gel forming abilities. Prepared formulations were evaluated for pre-compression properties like flow of granules, bulk and tapped density, post-compression properties like uniformity of weight, hardness, friability, thickness, *in-vitro* buoyancy characteristics, drug contenting-vitro drug release profile and mechanism of drug release. All the prepared batches showed good *in-vitro* buoyancy. It was also found that *in-vitro* drug release on increasing the amount of natural

retardant polymer mango resin. The kinetic of drug release from all the formulations followed the zero by regression analysis and further mechanism of drug release was confirmed by Higuchi's and Korsemeyer's model showed that non-fickian and anomalous drug release. Finally optimized formulation was compared with marketed SR tablet which showed similarity factor value 75.35.

AIM AND OBJECTIVE

- To design, formulate & evaluate floating matrix tablets containing Ezetimibe based on effervescent technology in order to increase gastric retention time.

- To evaluate the influence of preparative parameter and its effect on drug release and floating ability of the formulation.

- To evaluate the in-vitro release profile of Ezetimibe and evaluate the release mechanism on the basis of various kinetic models.

- To evaluate the stability studies for samples which analysed for drug content, characteristics and in-vitro dissolution studies.

PLAN OF WORK

1. Literature review
2. Pre-formulation studies
3. Preparation of tablets by direct compression method
4. Evaluation of tablets for:

a. Hardness

b. Thickness

c. Friability

d. Weight variation

e. Content uniformity

f. Assay

g. Floating lag time

h. Floating duration

i. Matrix integrity

j. Dissolution studies

5. Kinetic model analysis

a. First order

b. Zero order

c. Higuchi model

d. Korsmeyer-peppas model

6. Stability studies

DRUG PROFILE

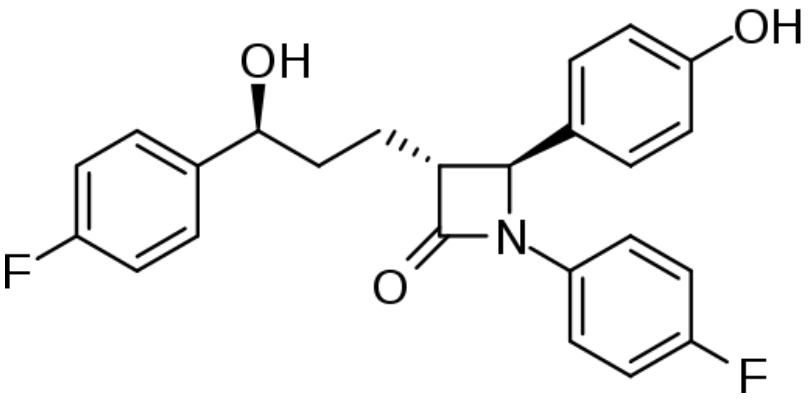
Ezetimibe[33][34]

Chemical IUPAC : (3R, 4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-

-3- hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one

Empirical Formula : $C_{24}H_{21}F_2NO_3$

Structural Formula :



Molecular weight : 409.4 g/mol

Description : white fine powder

Storage : Store at 25 C (59-86 F)

Melting point : 164 to 166 C

Solubility : Insoluble in water and soluble in methanol

Mechanism of Action:

Ezetimibe inhibits the absorption of cholesterol from the small intestine and decreases the amount of cholesterol normally available to liver cells, leading them to absorb more from circulation and thus lowering levels of circulating cholesterol.

Dosing:

10mg once daily

PHARMACOLOGY:

Pharmacodynamics:

Eztimibe is a drug that lowers plasma cholesterol levels. It acts by decreasing cholesterol absorption in the small intestine. Ezetimibe is recommended as second line therapy for those intolerant of statins or unable to achieve the target LDL cholesterol levels by statins alone.

Ezetimibe is indicated in the United States as an add-on to dietary measures to:

- Reduce levels of certain lipids in people with primary hyperlipidemia, alone or with a statin;
- Reduce levels of certain lipids in people with primary hyperlipidemia alone or with a statin;
- Reduce levels of certain lipids in people with mixed hyperlipidemia, in combination with fenofibrate;
- Reduce levels of certain lipids in people with homozygous familial hypercholesterolemia, in combination with specific statins;
- Reduce levels of certain lipids in people with homozygous sitosterolemia.

Pharmacokinetics:

Absorption:

Within 4-12 hours of the oral administration of a 10mg dose to fasting adults, the attained mean ezetimibe peak plasma concentration (C_{max}) was 3.4-5.5 mg/ml. Following oral administration, ezetimibe is absorbed and extensively conjugated to a phenolic glucuronide (active metabolite).).

Metabolism

Ezetimibe is primarily metabolized in the liver and the small intestine via glucuronide conjugation with subsequent renal and biliary excretion.

Distribution

Mean $C_{(max)}$ (45-71 mg/ml) of ezetimibe- glucoronide is attained within 1-2hrs. Ezetimibe and its active metabolites are highly bound to human plasma proteins (90%). The bioavailability of the drug is 35-65%.

Excretion

Ezetimibe is excreted 11% in renal and 78% in fecal matter. Both the parent compound and its active metabolite are eliminated from plasma with a half-life around 22 hours, allowing for once-daily dosing.

INDICATIONS AND USAGE:

- Indicated in the treatment of hypercholesterolemia

Contraindications:

- Previous allergic reaction including rash, angioedema and anaphylaxis and severe liver diseases when taken with a statin.
- Ezetimibe may have significant medication interactions with cyclosporine and with fibrates other than fenofibrate.

ADVERSE EFFECTS:

Common adverse effects associated with ezetimibe include headache or diarhoea. Infrequent adverse effects (0.1-1% of patients) include: myalgia or raised liver function test (AST/ALT) results. Rarely(<0.1 % of patients), hypersensitivity reactions (rash, angioedema) or myopathy may occur.

POLYMER PROFILE

HPMC[35]

Nonproprietary Names:

- JP: Hydroxypropylmethylcellulose
- BP: Hypromellose
- PhEur: Hypromellose

Synonyms:

Benecel MHPC; E464; hyrodxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur

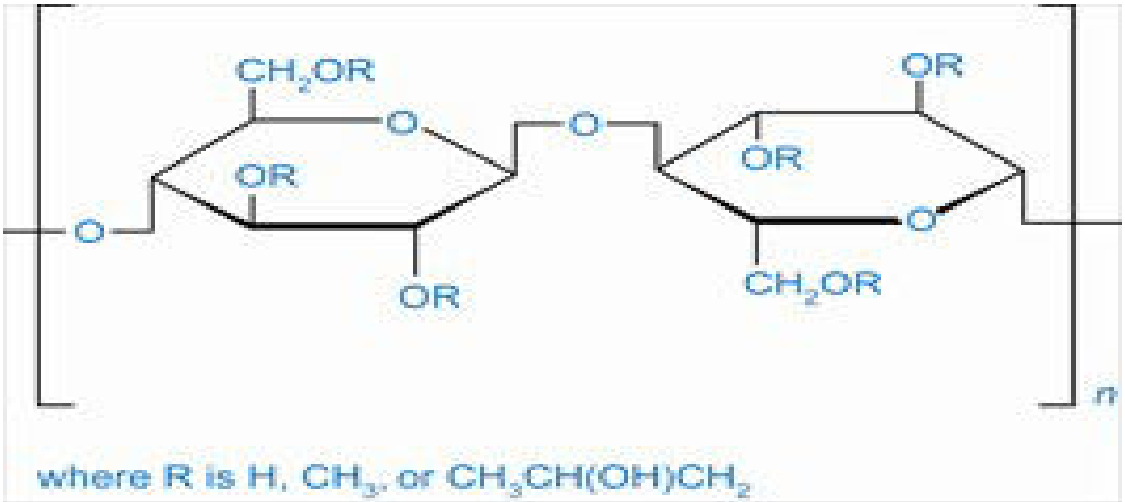
Chemical name and CAS Registry Number:

Cellulose hydroxypropyl methyl ether[9004-65-3]

Empirical formula and Molecular weight:

The PhEur 2005 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in a several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20^0c. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: eg; hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to approximate percentage content of the hydorxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. It contains methoxy and Hydroxypropoxy group.

Structural formula:



Functional category:

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of the film coating materials that are commercially available include *AnyCoat C, Spectracel*, and *Pharm coat.* Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45-1.0%w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. Hypromellose is also used

as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formations of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses.

Description:

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

Typical properties:

Acidity/alkalinity: pH=5.5-8.0 for a 1% w/w aqueous solution

Auto ignition temperature: 360^0C

Density (bulk): 0.341 g/cm^3

Density (tapped): 0.557 g/cm^3

Density (true): 1.326g/cm^3

Melting point: Browns at 190-200^0C; chars at 225-230^0C. Glass transition temperature is 170-180^0C.

Moisture content: Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 126

Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in such as ethanol and propan-2-ol provided the alcohol content is less than 50%w/w.

Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous, increasing concentration also produces more viscous solutions.

Table 4: Typical viscosity for 2%(w/v) aqueous solutions of Methocel (Dow Chemical Co)

Viscosities measured at 20^0C

Methocel product	USP 28 Designation	Nominal viscosity(mPa s)
Methocel K15M Premium	2208	4000
Methocel K50M Premium	2208	15000
Methocel K100M Premium	2208	100000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90^0C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume. When a water-miscible organic solvent such as ethanol (95%), glycol, or mixtures of ethanol and dichloromethane are used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

Stability and Storage Conditions:

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-90^0C, depending upon the grade and concentration of the material.

Incompatibilites:

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

MATERIALS AND METHODS

Table-3: Instruments used

INSTRUMENTS	MANUFACTURERS
Single pan analytical balance	Shimadzu corporation- Japan
FT/IR Spectroscopy/4100	Jasco, Johannesburg, South Africa
Tablet compression machine	(Rimek-MINI PRESS-II MT) Karnavati engineering Ltd-Gujarat
Hydraulic/pellet press	Kimaya engineer, Thane, India
Pfizer hardness tester	Shreeji scientific &laboratory instruments-Mumbai
Roche Friabilator	(Thermonik C-FTA20), Campbell electronics- Mumbai
Tap Density Apparatus	(Thermonik) Campbell electronics-mumbai
Vernier Calliper	Electro lab-mumbai
Dissolution Apparatus	Tab Machines, Mumbai, India
UV spectrophotometer	Shimadzu, Shimadzu Corporation, Philippines
Stability Chamber	Technico Chennai, India

Table 4: Materials used

MATERIALS	SUPPLIERS/MANUFACTURER
Ezetimibe	Bafna Pharmaceuticals Ltd-Chennai
HPMC K4 (Methocel)	Colorcon Asia Pvt Ltd
HPMC K15(Methocel)	Colorcon Asia Pvt Ltd
HPMC K100(Methocel)	Colorcon Asia Pvt Ltd
Pregelatinized Starch	Colorcon Asia Pvt Ltd
Sodium bicarbonate	SD fine chemicals-Mumbai
Cross povidone XL 10	Bafna Pharmaceuticals Ltd, Chennai
Magnesium Stearate	Loba Chemie-Mumbai

METHODOLOGY:

PRELIMINARY STUDIES

Preparation of standard stock solution[36]:

The standard stock solution was prepared by dissolving 10mg of the drug in 5ml of methanol to get a concentration of 1000mcg/litre. It was appropriately diluted with methanol to get a concentration of 100mcg/litre and was kept as stock solution.

Determination of λmax:

The standard solution of Ezetimibe was scanned in the UV spectrophotometer to obtain the maximum wavelength of absorption against blank between wavelengths of 200-400nm. The standard solution was scanned for absorbance maxima against blank. The maximum absorbance was found to be 233nm.

Preparation of calibration curve:

The stock solution of ezetimibe was accordingly diluted to obtain concentration range of 0-10µg/ml. The absorbance was observed against methanol as blank and the calibration curve was plotted between concentration (x-axis) and absorbance (y-axis).

FORMULATION OF FLOATING MATRIX TABLETS:

POLYMER SELECTION[38]:

Trial batches of ezetimibe floating matrix's tablets were prepared using different polymers (HPMC K4, HPMC K15, HPMC K100, sodium bicarbonate, PG Starch); drug polymer ratio of (1:1) was used. Tablets prepared by direct compression technique and evaluated for floating lag time and matrix integrity in HCl and 2% Sodium lauryl sulphate medium.

FORMULATION DESIGN

Floating matrix tablets of Ezetimibe were formulated based on effervescent technique using

- Matrix forming swellable polymer: HPMC K4, HPMC K15, HPMC K100
- Effervescent compounds: Sodium Bicarbonate
- Filler: Pregelatinized Starch

Tablets were prepared by direct compression method. A total of 6 formulations were designed by varying the amounts of polymer and sodium bicarbonate.

Table 5: Formulation table of floating Tablets of Ezetimibe

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)

Ezetimibe	10	10	10	10	10	10
Cross povidone	2	2	2	2	2	2
PG Starch	19.45	19.45	19.45	13.45	13.45	13.45
HPMC K4	25	30	-	-	-	-
HPMC K15	-	-	25	30	-	-
HPMC K100	-	-	-	-	25	30
Sodium bicarbonate	2	2	2	3	3	3
Sodium Lauryl Sulphate	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium Stearate	0.35	0.35	0.35	0.35	0.35	0.35

PREFORMULATION STUDIES[38][39]

The discovery and development of new chemical entities(NCEs) into stable, bioavailable, marketable drug products is a long but rewarding process. Once a NCE is selected for development, choosing the molecular form that will be an active pharmaceutical ingredient (API) is a critical milestone because all subsequent development will be affected by this decision. A well- designed preformulation study is necessary to fully characterize molecules during the discovery and the development process. The procedure of each preformulation tests suitable for tablets is given below:

DRUG-EXCIPIENT COMPATIBILITY STUDY BY FTIR

IR spectra matching approach was used for determination of any possible chemical interaction between drug and polymers. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form transparent pellets using a hydraulic press at 6 tons pressure. It was then scanned from 4000 to 400 cm^{-1} in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers; matching was done to detect any appearance or disappearance of peaks.

PREPARATION OF POWDER BLEND:

The ingredients were accurately weighed and shifted to sieve #60, and then the materials except talc and magnesium stearate were blended using mortar and pestle for 10 min in an ascending order. Powder mixture then blended with talc and magnesium stearate for 5 minutes.

EVALUATION OF POWDER BLEND:

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated. While the flow properties of the powder blend were accessed from the angle of repose.

1. **Bulk density and tapped density[40]:**

Both loose bulk density(LBD) and tapped bulk density(TBD) were determined. Accurately weighed amount of granules were taken in a 25ml measuring cylinder of Borosil and measured/recorded for the volume of packing, then tapped 100 times on a plane hard wooden surface and tapped volume of packing recorded.

LBD and TBD was calculated using the following formula:

$$\textbf{LBD(Loose Bulk Density)} = \frac{\textbf{Mass of Powder}}{\textbf{Volume of packing}}$$

$$\textbf{TBD(Tapped Bulk Density)} = \frac{\textbf{Mass of Powder}}{\textbf{Tapped Volume of Packing}}$$

2. **Compressibility index:**

Percentage compressibility of powder mix was determined by Carr's compressibility index. Grading of the powders for their flow properties according to arr's index is calculated by following formula.

$$\text{Carr's Index \%} = \frac{\text{TBD- LBD}}{\text{TBD}} \times 100$$

Table: 6 Scale of flowability based on Compressibility Index

COMPRESSIBILITY INDEX	FLOW CHARACTER
≤ 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very Poor
≥ 38	Very, very Poor

3. **Angle of repose**

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h/r$$

Where,

θ is the angle of repose,

h is the height and

r is the radius

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Table 7: Flow properties and corresponding angles of repose

FLOW PROPERTY	ANGLE OF REPOSE(DEGREES)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very Poor	56-65
Very Very Poor	>66

Hausner's Ratio:

Hausner's ratio is the ratio of bulk density to the tapped density of powder (or) initial volume of the powder mass to the final volume of the powder mass obtained after specified number of tapping.

Table 8: Scale of flowability based on Hausner's Ratio

HAUSNER'S RATIO	FLOW CHARACTER
1-1.1	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very Poor
≥ 1.60	Very, very Poor

COMPRESSION OF FLOATING MATRIX TABLET[41]

About 60mg of the mixture blend was weighed accurately and fed into the die of single punch tablet press and compressed at 1.5N compression force using 6.5mm flat punches.

EVALUATION OF FLOATING MATRIX TABLETS:

1.Weight variation test[41]:

20 tablets were selected randomly and weighed. Average weight was calculated. Each tablet was weighed individually. Weight of the individual tablet was compared with the average weight and reported with standard deviation. The tablets meet the USP requirements if not more than two tablets are outside the percentage limits and if no tablet differs by more than two times the percentage limit.

Table 9: Weight Variation limit of tablets

Average weight of tablets	Percentage Deviation
130mg or less	± 10%
More than 130mg but less than 324mg	± 7.5%
More than 324mg	± 5%

2.Thickness and diameter:

Thickness and diameter were measured during tablet compression using digital vernier caliper.

3. Hardness[42]:

Hardness of a tablet can be determined by using Pfizer or Monsanto hardness apparatus. The pressure required to break the tablet into fragments is determined. The minimum value required for a tablet is $4kg/cm^2$.

4. **Friability:**

Friability is performed to evaluate the ability of the tablet to withstand abrasions. It can be determined by using Roche's friabilator. Ten tablets were weighed and placed in the tumbling chamber which was rotated for 100 revolutions. The tablets were deducted and again weighed. The loss in weight indicated the friability.

$$\text{Percentage friability} = \frac{A-B}{B}$$

Where A = initial weight of the tablet

B = weight of tablet after 100 revolutions.

5. **Assay of Tablet[43]:**

- **Preparation of Diluent:**

Buffer:Aceto Nitrile (40:60)

- **Preparation of Buffer:**

Dissolve 250mg of Heptane 1-sulfonic acid of sodium salt in 500ml of water.

The concentration of the sample is 10ppm. The measurement of absorption was found to be 235nm.

6. **In-vitro Dissolution[44]:**

Ezetimibe release from different formulations were determined using a USP XXIII paddle apparatus 2 under sink condition. To stimulate in-vivo condition the dissolution medium was selected as 900ml HCl buffer with 2% SLS at 37±0.2^{0}C. all experiments were done in triplicate and average values were taken. The formulations prepared were subjected to dissolution tests for 8hrs. Sample were withdrawn at predetermined time intervals, filtered through 0.45µm whatman filtr paper and replaced by an equal volume of dissolution medium. Absorbance of the diluted samples were determined by UV spectrophotometer at 233nm and drug content was calculated using calibration curve method.

Dissolution test conditions:

Apparatus : USP XXIII paddle apparatus 2

RPM : 100

Temperature : 37± 0..2^0 C.

Medium : HCl buffer + 2% SLS

Duration of test : 8hrs

Sampling intervals : Every one hour

Sampling volume : 10ml

Floating Behaviours[44]:

Floating behavior studies were carried out in a USP XXIII paddle apparatus 2 at a paddle speed of 100 rpm in 900ml HCl buffer(pH 1.2) + 2% SLS at 37±0.2^0 C. The parameters determined were; the time taken by the tablet to go upward and float on the surface (floating lag time), the time at which the tablet remained buoyant (floating lag time), the time at which the tablet remained buoyant (floating duration) and relative matrix integrity (determined on the basis of visual inspection).

Related substances:

The test for related substances was carried out to detect the presence of impurities. The sample was made up with a concentration of 10ppm. It was validated with HPLC method against system suitability parameters.

DRUG RELEASE KINETICS[45][46]

To study the release kinetics, data obtained from in-vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released Vs time, first order as log cumulative percentage of the drug remaining Vs time, Higuchi's model (Equation 2) as cumulative percentage of drug released Vs square of time.

$$C = K_0 t \quad \text{---------- (1)}$$

Where,

K_0 : is the zero-order rate constant expressed in units of concentration/time

t : is the time in hours

A graph of concentration Vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

$$\mathbf{LogC = Log\ C_0 - Kt/\ 2.303} \quad \text{---------- (2)}$$

Where

$\mathbf{C_0}$: is the initial concentration of drug,

K : is the first order constant, and t is the time

$$\mathbf{Q = Kt^{1/2}} \quad \text{---------- (3)}$$

Where,

K : is the constant reflecting the design variables of the system

t : is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets

The data were also plotted using the Hixson- Crowell cube root law

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = KHC - t \quad \text{---------- (4)}$$

Where,

Q_t is the amount of drug released in time t,

Q_0 is the initial amount of the drug in the tablet and

KHC is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of the drug remaining in the matrix vs time.

Mechanism of Drug Release:

To evaluate the mechanism of drug release from Ezetimibe floating matrix tablet, data of drug release were plotted in Korsmeyer et al's equation (equation 5) as log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$Mt - M\infty = Kt^n \quad \text{---------- (5)}$$

Where,

$Mt/M\infty$ is the fractional solute release,

t is the release time,

K is a kinetic constant characteristic of the drug/polymer system, and

n is an exponent that characterizes the mechanism of release of tracers.

For cylindrical matrix tablets, if the exponent n= 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45≥ n≥ 0.89, then it is non-Fickian or anomalous diffusion, an exponent value of 0.89 is indicative of case-II transport or typical zero-order release.

STABILITY STUDIES[47]

Stability of a drug in its dosage form at different environmental conditions is important, because it determines the expiry date of that formulation. Hence, the stability of the drug in the floating matrix tablet was studied. Stability studies were conducted according by storing the tablets at 40^0C± 2^0C, 70 % RH± 5% for 45 days. The samples were withdrawn at initial, 30^{th} & 45^{th} day and analyzed suitably for the physical characteristics, drug content and cumulative release.

RESULTS

PRELIMINARY STUDIES

Determination of λmax of Ezetimibe:

Ezetimibe showed absorption maxima at 233nm.

Table 10: Calibration curve of ezetimibe at 233nm:

Concentration(µg/ml)	Absorbance
2	0.178
4	0.319
6	0.492
8	0.653
10	0.791

Fig 5: Calibration curve of Ezetimibe

Compatibility Studies by FTIR:

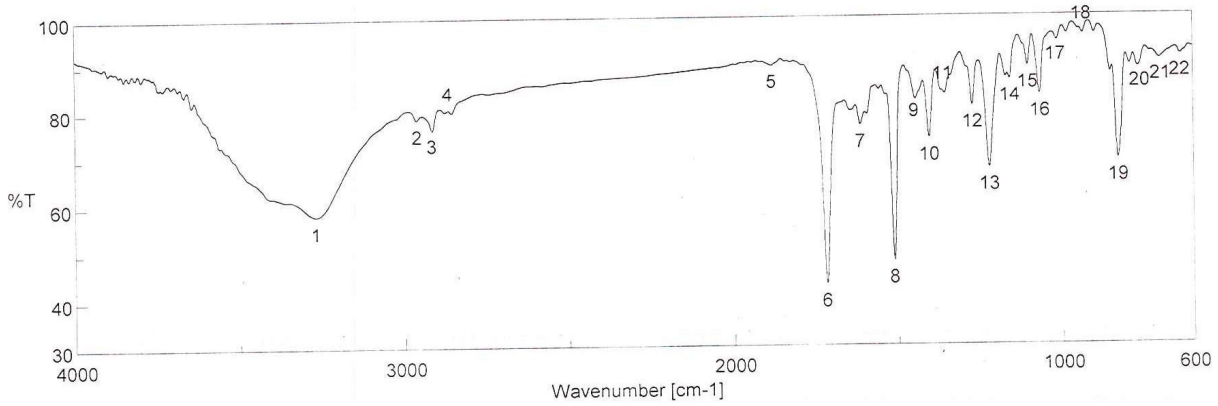


Fig 6:IR Spectra of Ezetimibe pure drug

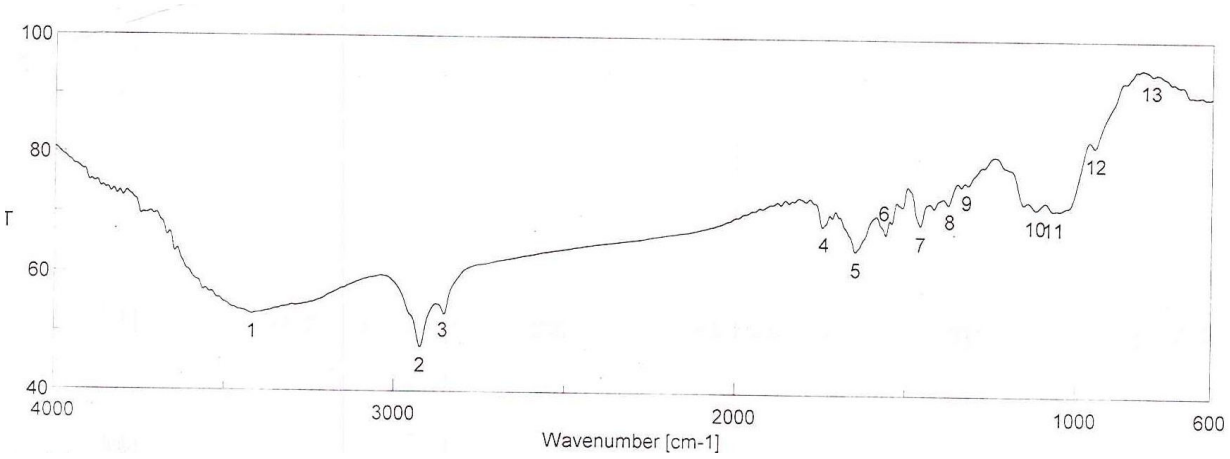


Fig 7: IR spectra of HPMC K100

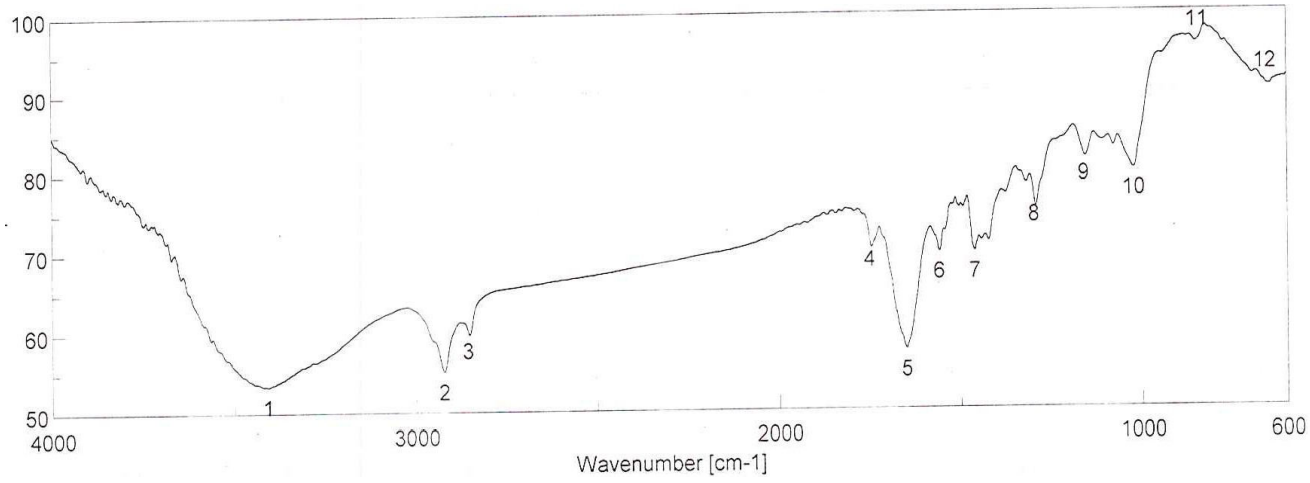


Fig 8: IR spectra of all excipients

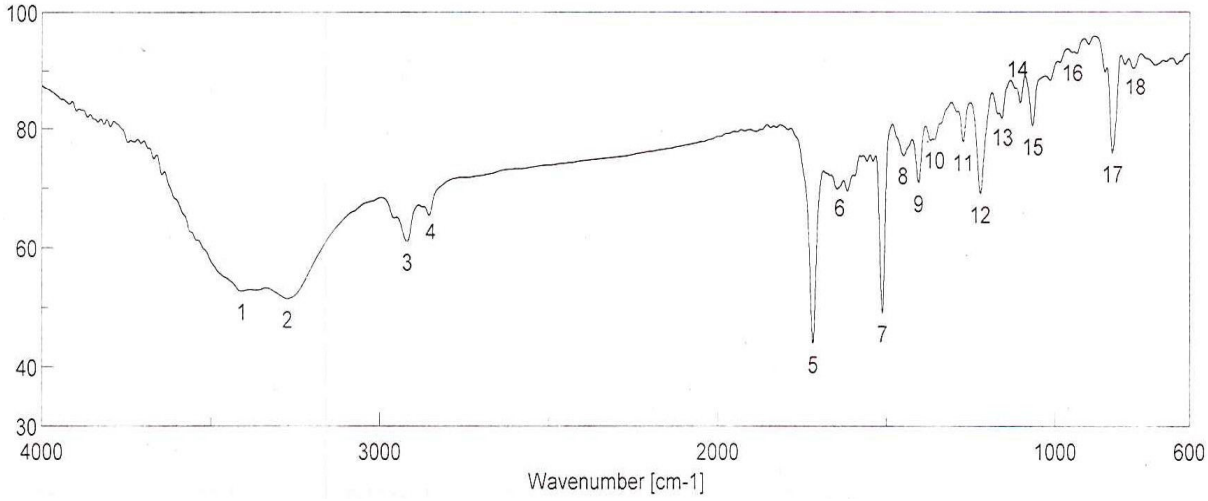


Fig 9: IR spectra of Ezetimibe + HPMC K100

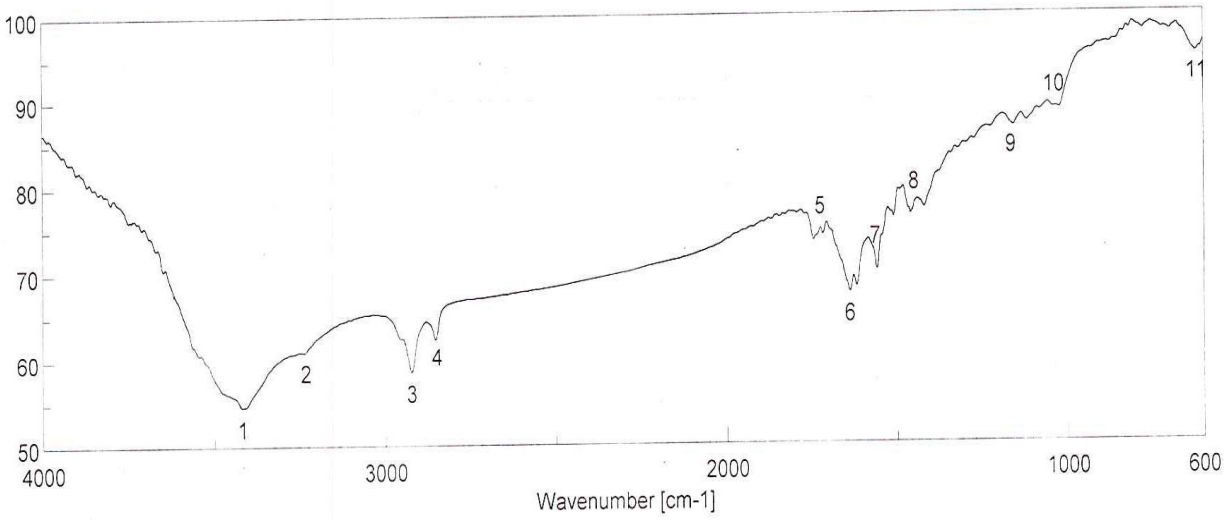


Fig 10: IR spectra of Ezetimibe + All excipients

Table 11: Characteristic peaks of Ezetimibe and its excipients:

Drug and Excipients	Interpretations					
	Substituted Aromatic Ring	**C=N stretching**	**C=O stretching**	**C=F stretching**	**OH**	**C--H stretching**
Ezetimibe	830.205	1512.4	1272.31	1404.41	3270.68	1718.26
Ezetimibe + HPMC K 100	830.205	1511.92	1272.31	1404.41	3409.53	1717.78
Ezetimibe + all excipients	846.115	1564.47	1165.76	1451.17	3418.21	1726.94

PRECOMPRESSION EVALUATION:

Evaluation of powder blend:

Table 12: Results of pre formulation studies of the blend

Formulation	Angle of repose (θ)	Bulk Density (g//cm$^{3)}$	Tapped Density (g/cm^3)	Hausner's Ratio	Compressibility/ Carr's Index
Pure Drug	$35^0$22'	0.254	0.625	2.46	59.36
F1	$24^0$13'	0.292	0.346	1.18	15.6
F2	$26^0$21'	0.284	0.335	1.17	15.2
F3	$25^0$19'	0.293	0.346	1.19	15.3

F4	$22^0$23’	0.280	0.321	1.14	12.7
F5	$26^0$12’	0.290	0.345	1.18	15.9
F6	$22^0$16’	0.296	0.340	1.14	12.9

POST- COMPRESSION EVALUATION OF FLOATING MATRIX TABLETS

Table 13 : Results of post compression parameters of the tablets

Formulation	Weight Variation (mg)*, n= 20	Hardness (kg/cm^2)	Thickness (mm)*, n=3	Friability (%)	Assay (% Drug Content)* n=3
F1	60±2.8	3.7	2.3	0.034	95.53
F2	59±1.9	3.6	2.1	0.033	98.35
F3	61±2.7	3.4	2.2	0.034	97.64
F4	60±2.2	3.5	2.1	0.034	98.13
F5	58±1.1	3.5	2.3	0.035	98.22
F6	59±3.7	3.6	2.1	0.032	97.34

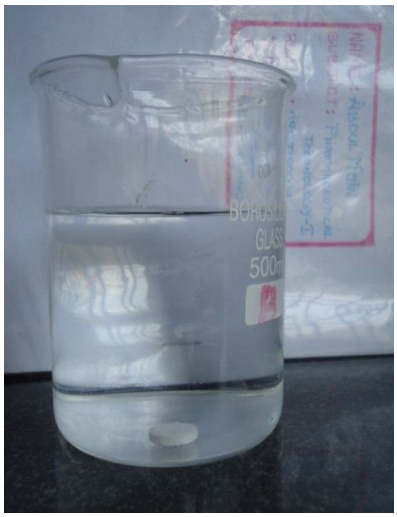
Evaluation of floating behaviour:

Table 14: Results of floating behaviour

Formulation	Floating lag time(s)	Buoyancy(hrs)	Matrix integrity*
F1	53	>12	++
F2	57	>12	++
F3	54	>12	++
F4	30	>12	++
F5	21	>12	++

F6	29	>12	++

***(-) poor, (+) moderate, (++) good, (+++) excellent**



Initial (F5) After 30s (F5)

Fig 12: *invitro* floating behaivour

Evaluation of *In- vitro* drug release

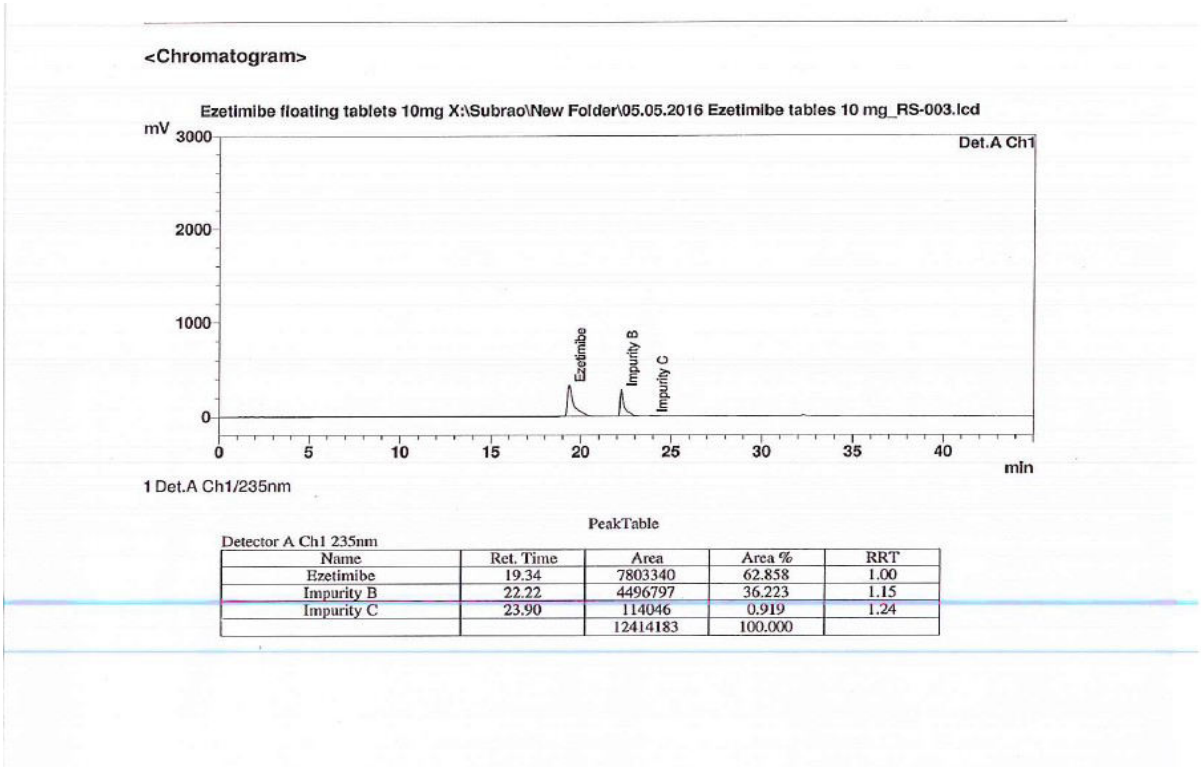
Time(hrs)	Cumulative Per cent Drug Release					
	F1	F2	F3	F4	F5	F6
1	26.93	39.34	24.9	17.54	20.85	24.17
2	37.33	46.56	35.2	31.30	33.3	33.64
3	45.79	51.25	47.49	39.12	41.4	38.18
4	50.13	57.42	55.44	47.53	49.56	50.22
5	59.21	64.45	64.45	60.28	59.23	61.93
6	64.89	70.45	72.45	70.87	63.21	72.45
7	71.45	79.67	84.67	80.21	78.23	83.53
8	91.89	85.31	93.12	89.21	96.82	90.12

Table 15: *In vitro* release of Ezetimibe floating tablets

Fig 13: *In-vitro* dissolution studies of F1,F2 and F3

Fig 14: *In-vitro* dissolution studies of F4, F5 and F6

RELATED SUBSTANCES

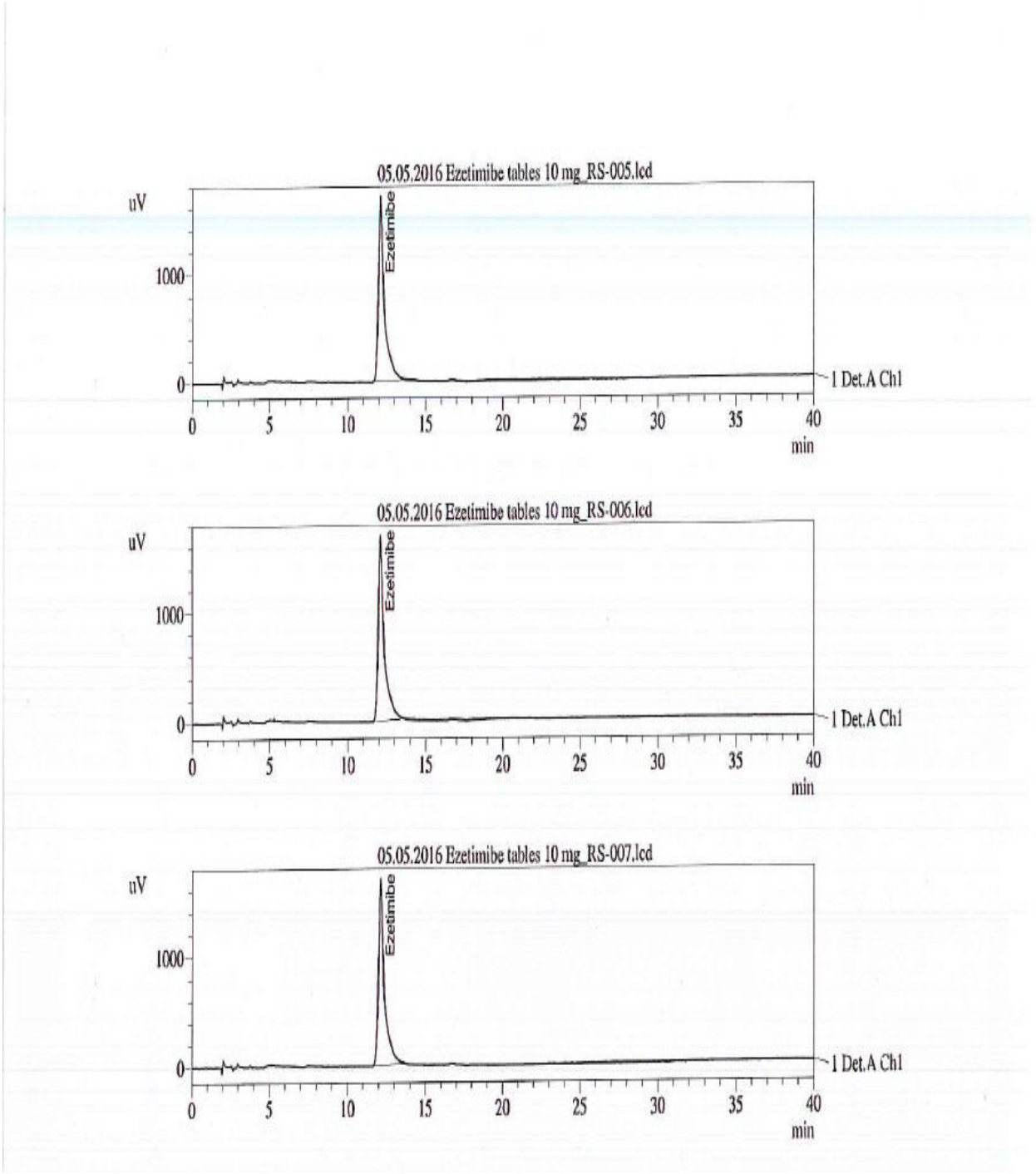


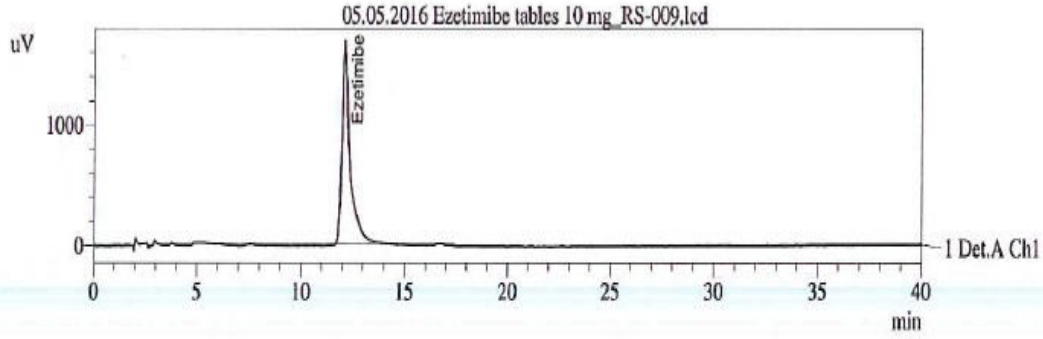
PeakTable

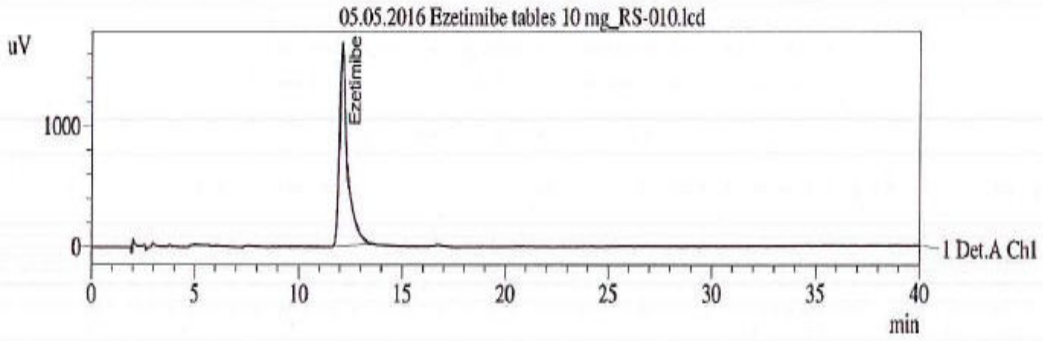
Detector A Ch1 235nm

Name	Ret. Time	Area	Area %	RRT
Ezetimibe	19.34	7803340	62.858	1.00
Impurity B	22.22	4496797	36.223	1.15
Impurity C	23.90	114046	0.919	1.24
		12414183	100.000	

Fig 15: Related substances of SST of Ezetimibe





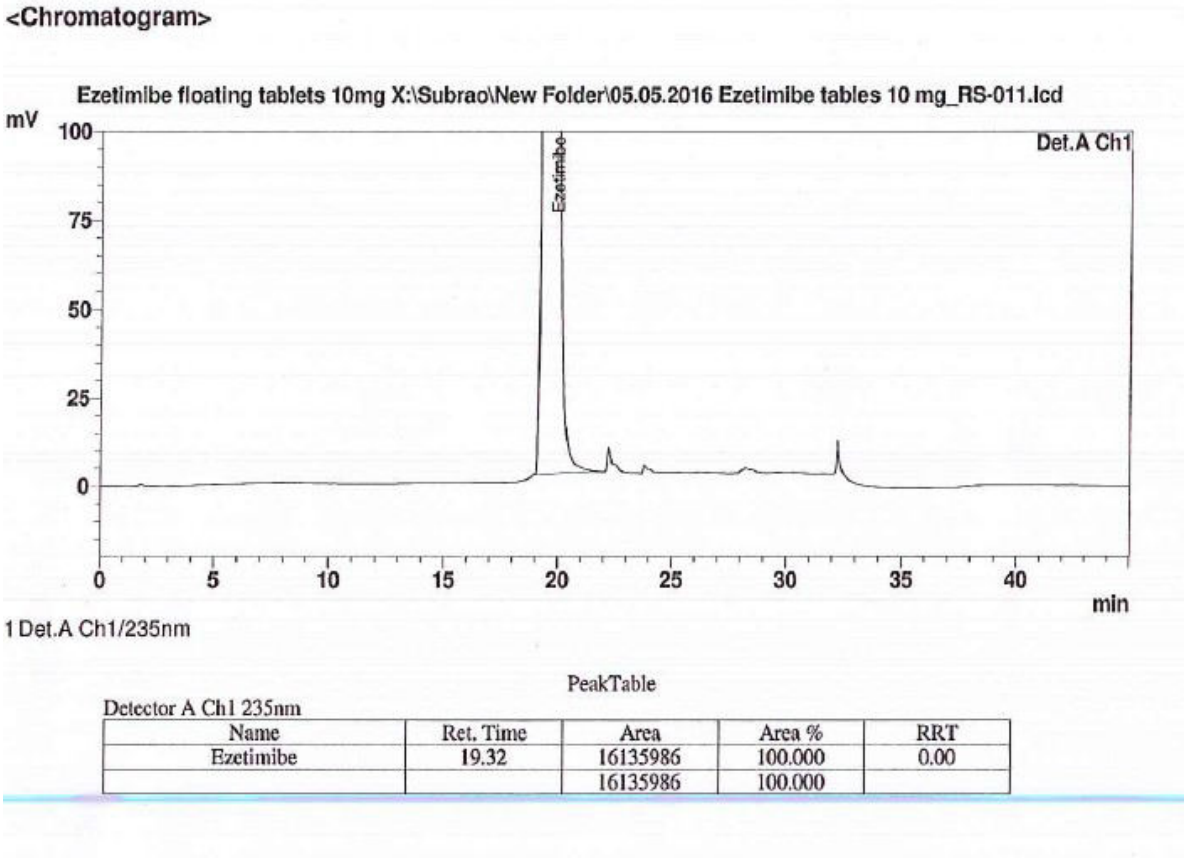


<< Detector A >>

ID#1 Compound Name: Ezetimibe

Title	Sample ID	Ret. Time	Area	T.Plates	T. Factor
05.05.2016 Ezetimibe tables 10 mg_RS-005.lcd	Standard_1	12.09	44806	7521	2.05
05.05.2016 Ezetimibe tables 10 mg_RS-006.lcd	Standard_2	12.09	44857	7418	2.02
05.05.2016 Ezetimibe tables 10 mg_RS-007.lcd	Standard_3	12.10	44596	7416	2.03
05.05.2016 Ezetimibe tables 10 mg_RS-008.lcd	Standard_4	12.10	44653	7411	2.03
05.05.2016 Ezetimibe tables 10 mg_RS-009.lcd	Standard_5	12.07	45185	7349	2.03
05.05.2016 Ezetimibe tables 10 mg_RS-010.lcd	Standard_6	12.08	44898	7366	2.01
Average		12.09	44833	7414	1.83
%RSD		0.10	0.47	0.81	0.73
Standard Deviation		0.01	209	60	0.01

Fig 16: Related Substances of Ezetimibe Standard



PeakTable

Detector A Ch1 235nm

Name	Ret. Time	Area	Area %	RRT
Ezetimibe	19.32	16135986	100.000	0.00
		16135986	100.000	

Fig 17: Related Substances of Ezetimibe sample

Table 16: Results of Related substances

Name	Retention time
Standard	19.34
Sample	19.32

RELEASE KINETIC ANALYSIS

Fig 18: plot of Zero order kinetics

Fig 19: plot of First order kinetics

Fig 20: Higuchi's plot

Fig 21: Korsmeyer - peppas model

Table 17: Results of kinetic analysis

Formulation	Zero order	First order	Higuchi model	Korsmeyer- peppas model	
	R^2	**R^2**	**R^2**	**n**	**R^2**
F1	0.973	0.621	0.936	0.935	0.959

STABILITY STUDIES

Table 18: Results of Stability Studies

Sl. No	Parameters	Initial	30^{th} day	45^{th} day
1	Physical appearance	White	White	White
2	Assay (% drug content)	98.22	98.25	98.25
3	Floating lag time (s)	31	32	30
4	Floating duration (hrs)	More than 8hrs	More than 8hrs	More than 8hrs
5	Cumulative % Drug release	96.82	95.12	95.32

DISCUSSION

PRELIMINARY STUDIES:

Determination of λ_{max} of Ezetimibe:

A solution containing (1mg/ml) of Ezetimibe was scanned in the range of 200-400nm. Ezetimibe showed absorption maxima at 233nm.

Calibration curve of Ezetimibe:

Calibration curve of Ezetimibe showed good linearity in the range of 10- 50µg/ml with Regression coefficient (R^2) value of 0.998 as shown in (fig. 5)

Compatibility studies by FTIR:

Drug polymer interaction was checked by comparing the IR spectra of pure drug with the IR spectra of physical mixture of drug and excipients used.

IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. All the characteristic peaks of Ezetimibe were also found in the IR spectra of physical mixtures.(Table 11)

Frequencies of functional groups of pure drug remained intact in physical mixtures containing different polymers. Hence there was no major interaction during the drug and excipients used in this study.

PRECOMPRESSION EVALUATION:

Evaluation of the powder blend:

All materials were properly mixed as per compostion shown in table(12). For each designed formulation, blend of drug and excipient were prepared and subjected to pre compression parameters like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio like the obtained results were shown in Table- 12

As a general guide, powders with angle of repose greater than 40^0C have unsatisfactory flow properties, whereas minimum angles close to 25^0 correspond to very good flow properties. The angle of repose range between $22^0$16' to $26^0$21', which indicates good flow properties of powders.

The bulk density and tapped density for all formulation were found to be in the range of 0.280 to 0.296 gm/cm^3 and 0.321 to 0.346 g/ cm^3 respectively, which indicates good packing character.

The powder has good flowability, when the Hausner's ratio is lower than 1.2 and when the value exceeds 1.2, it indicates poor flow. Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. A compressibility material will be less flowable, and the powders with compressibility values greater than 20-21 % have found to exhibit poor flow properties. The hausner's ratio and percentage compressibility index was found to be in the range 1.14 to 1.18 and 12.7% to 15.9% respectively, which supports the fact that these formulations have good flow and compaction properties.

All formulations exhibited good flow property and compressibility which is very essential for direct compression and hence tablet was prepared by using direct compression technology.

COMPRESSION OF TABLETS

The floating matrix tablets were prepared by direct compression technique. The target weight of the prepared tablet was 60mg. the desired hardness in between 3-5kg/cm^2. All the tablets were found to be uniform in size and shape and no processing problems were encountered during compression process.

POST-COMPRESSION EVALUATION OF FLOATING MATRIX TABLETS:

Evaluation of physical parameter:

The compressed tablets were evaluated for the weight variation, hardness, thickness, friability and content uniformity as per Indian Pharmacopoeia and the results were shown in table (13)

All the compressed tablets passed the weight variation test. The mean thickness of the prepared tablets was found to be in between 2.1 to 2.3mm. The mean hardness of the tablets ranged from 3.4 to 3.7 kg/ cm^2. Percentage friability ranged from 0.032% to 0.035 %. The drug content in all the prepared tablets complied with the Indian Pharmacopoeia requirements, which was found to lie within the range of 95.53% to 98.35%.

All values of the physical parameter were found to be within the Pharmacopoeial limits.

Evaluation of floating behaviours:

The parameters determined were:

Floating lag time – the time taken by the tablet to reach the surface and float.

Floating duration: the time at which the tablet remained buoyant, matrix integrity(determined on the basis of visual inspection); and the results were shown in (Table)

Sodium bicarbonate was used as the effervescent base. Upon contact with the acidic medium, the fluid permeated into the tablet, causing neutralization reaction to occur, which generates Carbon dioxide (CO_2). The swelling polymer traps the CO_2 so generated and thus provides continued buoyancy.

The floating lag time was found to be in the range of 29 to 53 seconds. Increase in the effervescent agent led to decrease in the floating lag time (table 14).

Formulations containing higher concentrations of polymer showed structural integrity and and buoyancy time of more than 12 hours.

Evaluation of in-vitro drug release:

Ezetimibe was released from different formulations as determined in 900ml HCl + 2% SLS medium at 37± 0.2^{0}C.

It was observed that as the concentration of polymer increases, the drug release is decreased. HPMC K4, HPMC K 15, HPMC K 100 being highly swellable polymers were able to swell to an considerable extent and thus concentration increased and thus forms a thick viscous layer around the matrix tablet.

Related Substances:

The formulation was evaluated for impurities by HPLC method. Since the retention time of the standard and sample is same i.e 19.32, the formulation was analysed to be pure.

DRUG RELEASE KINETICS:

The in-vitro drug dissolution data was analyzed for establishing kinetics of drug release. Model fitting was done (Zero- order, first-order, Higuchi, Korsmeyer-peppas model). Interpretations of data were based on regression coefficient. The kinetic analysis of the best formulation was shown.(Table 17).

The R^2 values obtained from zero order plots was found to be higher in comparison to first order plot which suggest that the drug release rate from the prepared tablets were in constant and controlled manner. The data suggest that most of the formulation fit into Higuchi's equation for the release of drug from the homogeneous polymeric matrix that depends mostly on diffusion characteristics.

Further to identify the release mechanism of ezetimibe from matrix tablets, the dissolution data were fitted to korsmeyer-peppas diffusion model. The 'n' values for HPMC K4, HPMC K100, HPMC 15 ranged from ($0.45<n<0.89$) which indicates that the release mechanism was non-fickian or diffusion.

STABILITY STUDIES:

Accelerated stability studies carried out according ICH guidelines. Optimized formulation (F5) were sealed in aluminium packaging coated inside with polyethylene, and kept in stability chamber at 40^0C ± 2 C and 75% ± 5% RH for 45 days. At the end of the period, sample were analysed for drug content, floating characteristics and in-vitro drug release as shown (Table 18).

Stability study of optimized formulation revealed no significant change in physical appearance, drug content, floating lag time, floating duration as well as *in- vitro* drug release. And hence the optimized formulation were found to be stable at 40 C ± 2 C and 75%± 5% RH for 45 days.

SUMMARY

The present study was aimed at preparing floating matrix tablets containing Ezetimibe based on gas formation technique in order to increase the gastric retention time for enhancing controlled release of the drug for a longer time. Ezetimibe shows pH dependent solubility and stability, it is more soluble and stable in acidic than alkaline pH. Hence, it will be beneficial to increase its gastric residence time.

FORMULATION DESIGN:

In this study, floating matrix tablets of Ezetimibe were prepared based on effervescent technique using HPMC K4, HPMC K15, HPMC K100 as (matrix forming swellable polymers), sodium bicarbonate (effervescent compound) and PG Starch. A total of 6 formulations were designed by varying the amounts of polymer and sodium bicarbonate at 2 levels (low and high) using cross over design.

PRE- COMPRESSION STUDIES:

The prepared powder blends of all the 6 formulations were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results obtained from these studies showed that the prepared blends were having satisfactory fluidity and compressibility; hence tablets can be prepared by direct compression method.

IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymers. This study revealed that there was no major interaction between the drug and excipients used.

COMPRESSION OF TABLETS:

The floating matrix tablets were prepared by direct compression technique using single punch tablet press at a compression force (1.5 N) in a concave punches (6.5mm). the target weight of the prepared tablet was 60mg. The desired hardness is between 3-5 kg/cm^2. All the tablets were found to be uniform in size and shape and no processing problems were encountered during compression process.

POST- COMPRESSION STUDIES:

The compressed tablets were evaluated for their weight variation, hardness, thickness, friability and content uniformity as per Indian pharmacopoeia and the results were found to be within the prescribed limits.

Floating behaviour were carried out in a USP XXIII paddle apparatus 2 at a paddle speed of 100rpm in 900ml HCl and 2% SLS at 37±0.2 C. The parameters determined were Floating lag time, Floating duration and Relative matrix integrity). Floating lag time for all formulation were found to be less than 5 minutes. Formulations containing high concentration of polymer showed structural integrity and buoyancy time of more than 12 hrs, while others formulations, while others formulations showed rapid disintegration on contact with dissolution media.

Ezetimibe release from different formulations was determined using a USP XXIII paddle apparatus 2 at paddle speed of 100rpm in 900ml HCl buffer (pH 1.2) at 37±0.2 C under sink condition for 10hrs. In this study, it was observed that as the concentration of polymer increase, the drug release decreases.

The *in vitro* drug dissolution data obtained for the best formulation were plotted in various kinetic models for establishing kinetics of drug release. Zero order plot suggests that the drug release rate from the prepared tablets were in constant and controlled manner. The data also suggest that the formulation fit into Higuchi's equation for the release of the drug from the homogeneous polymeric matrix that depends mostly on diffusion characteristics. From the korsmeyers- peppas diffusion model the release mechanism of Ezetimibe from matrix was found to be Case- II Transport or typical zero order release.

The test for Related substances was carried out for the optimized formulation and it was found that the formulation was free from impurities.

Accelerated stability studies were carried out for the optimized formulation (F5) in a stability chamber at 40 C ± 2 C and 75% ± 5% RH for 45 days . The study showed no significant change in physical appearance, drug content, floating lag time, floating duration as well as *in-vitro* drug release, hence the formulation was found to be stable.

CONCLUSION

In the present study, floating matrix tablets have been formulated with Ezetimibe with the help of polymers such as HPMC K4, HPM C K 100 and HPMC K 15. Effervescent technique was used to keep the tablets floating over the simulated gastric fluid (pH 1.2) for 24 hrs. All the formulations showed floating lag time less than 1 minute. Sodium bicarbonate was found to be good effervescent base. The drug release mechanisms for this formulation was found to be of zero order and diffusion. The formulation F5 was selected as optimized formulations because it gave the best results in terms of the required *in-vitro* buoyancy as well as drug release in sustained manner and was also found to be stable under stability conditions.

Thus, the results of the current studies indicates, a promising potential of ezetimibe floating matrix tablet as an alternative to conventional dosage form. Further, clinical studies are needed to assess the utility of this system for patient suffering from hypercholesterolemia.

BIBLIOGRAPHY

1. Amit Kumar Nayak, Ruma Maji, Biswarup Das. Gastroretentive drug delivery systems: a review. Asian journal of pharmaceutical and clinical research, (2010), 3(1): 2-10

2. Brahma N Singh, Kwon H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of controlled release, (2000), 63:235-259

3. Pooja Mathur, Kamal saroha, Navneet syan, Surrender verma and Vipin Kumar, Floating Drug Delivery System : an innovative acceptable approach in gastro retentive drug delivery. Archives of Applied Science Research, (2010), 2(2) : 257-270

4. Rohit D Jhondale, Pallavi S Gadhave, Ashish A Mahajan, Mohini S Bodhane. Floating Drug Delivery System: A Review. World Journal of Pharmacy and Pharmaceutical Sciences, 4 (10): 562-575.

5. R Garg, G D Gupta. Progress in Controlled Gastroretentive Delivery Systems. Tropical Journa of Pharmaceutical Research, (2008), 7(3): 1055-1066.

6. KPR Choudhary, C.H.K.L Chaitanya. Recent Research on Floating Drug Delivery Systems – A Review. Journal of Global Trends in Pharmaceutical Sciences. (2014), 5(1): 1361-1373.

7. Sandina Swetha, Ravi Teja Allena, D V Gowda. A Comprehensive Review on Gastro retentive Drug Delivery Systems. International Journal of Research and Pharmaceutical Biomedical Sciences. (2012), 3(3): 1285- 1293.

8. Azhar Danish Khan, Meenakshi Bajpai. Floating Drug Delivery System: An Overview. IJPRIF. (2010), 2(4): 2497-2505.

9. Praveen Nasa, Sheefali Mahant, Deepika Sharma. Floating Systems: A Novel Approach Towards Gastroretentive Drug Delivery Systems. International Journal of Pharmacy and Pharmaceutical Sciences. (2010), 2(3): 2-7.

10. K.P.R Chowdary, K Ravi Shankar, Vijay Teeda. Floating Drug Delivery Systems-A Review of Recent Research. International Research Journal of Pharmaceutical and Applied Sciences. (2014), 4(2): 14-24

11. Akash Yadav and Dinesh Kumar Jain. Formulation development and characterization of propanalol hydrochloride microballoons for gastro retentive floating drug delivery. African Journal of Pharmacology, (2011), 5(15): 1801-1810.

12. Mayavanshi AV and Gajjar SS. Floating drug delivery system to increase the gastric retention of drugs: A review. Research journal of Pharmacy and Technology, (2008), 1(4) : 345-348.

13. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics. (2000); 195: 125-135.

14. Shanti Sagar, Srividya. L, B.K Nanjawade. Formulation and Evaluation of Gastro retentive Floating tablet of Quetiapine Fumerate. Indo American Journal Of Pharmaceutical Sciences. (2015), 2(5), 912-925.

15. Piyush Patel, Dinesh Puri, Anil Bhandari, Deepak Choudhary, Rambabu Sharma, Vivek Bhatele. Formulation and Evaluation of Chronomodulated Floating rug Delivery System

of Famotidine. FABAD J.Pharm.Sci, (2011), 36, 167-180.

16. Ying – Chen Chen, Lin-Wen-Lee, Hsiu-O HO, Chen Sha, Ming-Thau Sheu. Evaluation of water uptake and Mechanical Properties of Blended Polymer Films For Preparing Gas-generated Multiple-Unit Floating Drug Delivery Systems. American Pharmacists Association J Pharm Sci.2012), 101:3811-3822.

17. Rajani Shakya, Panna Thapa, Ranendra N. Saha. *In vitro* and *in vivo* evaluation of gastro retentive floating drug delivery system of ofloxacin. Asian Journal of Pharmaceutical Sciences(2013), 8, 191-198.

18. Govikari Koteshwar Rao, Praveen Kumar Mandapalli, Rajendraprasad Manthri, Veerareddy Prabhakar Reddy. Development and *in vivo* evaluation of gastro retentive delivery systems for cefuroxime axetil. Saudi Pharmaceutical Journal(2013) 21, 53-59.

19. Friederike Eisenacher, Grzegorz Garbacz, Karsten Mader. Physiological relevant *in vitro* evaluation of polymer coats for gastro retentive floating tablets. European Journal of Pharmaceutics and Biopharmaceutics (2014) , 1-9

20. Chandrasekhara Rao Baru, S Vidyadhara, KV. Raghavendra Rao, K Vanitha Prakash, B. Umashankar. Formulation and Evaluation of Ibuprofen Floating Tablets. International Journal of Pharmaceutical, Chemical and Biological Sciences (2012) , 2 (4), 472-481

21. Navjot Singh, Anirbandeep Bose, Rakesh K Mishra, Vivek Jain, Sanjay Dhakar, Dileep Bharati. Development and Evaluation of Gastro retentive Floating Drug Delivery system for Tizanidine Hydrochloride and its *in-vivo* gamma- scintigraphic studies using TC-99M Tracer. Asian Journal of Pharmaceutical and Clinical Research (2012) 5(3), 56-61

22. Mudgal Vinod Kumar, Kheri Rajat, Saraogi G.K. Singhai A.K, Sharma Dharmendra. Formulation and Evaluation of Sustained-release Floating tablets of Ciprofloxacin. International Research Journal of Pharmacy(2012), 3 (9). 120-122

23. Lingam Meka, Bhaskar Kesavan, Krishna Mohan Cinnala, Venkateswarlu Vobalaboina, Madhusudan Rao Yamsani. Preparation of a Matrix Type Multiple- Unit Gastro retentive Floating Drug Delivery System for Captopril based gas formation technique: *In vitro* evaluation. AAPS PharmSciTech (2008), 9(2) 612-619.

24. Suraj Aghav, Avinash Kondalkar, Navjyot Singh. Formulation and Optimization of Floating Drug Delivery System of Simvastatin. Asian Journal of Pharmaceutical Education and Research (2014), 3(4) 29-121

25. Garje Pravin K, Ratnaparkhi Mukesh P, Khade Ravindra B, Suryawanshi Akshay, Somvanshi Fattesingh U. Formulation and Evaluation of sustained release floating drug delivery system of metoprolol tartrate. International Journal of Drug Delivery and Research (2013), 5 (4), 178-186.

26. Aleksandar Alsovski, Emina Zahirovic, Amra Demirovic, Emilija Spaseska Aleksovska. Formulation and Evaluation of Effervescent Gastro retentive Floating tablets for Controlled Release of an Anti-ulcer Compound. International Journal of Pharmaceutics (2013), 3 (1) 23-30

27. M.A Hassan. Design and Evaluation of a floating Ranitidine tablet as a drug delivery system for oral application. Journal of Drug Delivery of Science and Technology (2007), 17(2) 125-128

28. Dave BS, Amin AF and Patel Mm. Gastro retentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. AAPS PharmSci Tech. 2004; 5(2); 1-6.

29. Ali Kadivar, Behnam Kamalidehghan, Hamid Akbari Javar, Ehsan Taghizadeh Davuodi, Nurul Dhania Zaharuddin, Bahareh Sabeti, Lip Yong Chung, Mohammed Ibrahim Noordin.

30. Pramod Patil, Someshwara Rao B, Suresh Kulkarni V, Basavaraj, Chetan Surpur, Anand Ammanage. Formulation and 1(1) : 17-22

31. Thakur Nasa, Sheefali Mahant. Floating Drug Delivery System using Methocel K100M and E50: Formulation and Characterization. *Acta Pharmaceutica Sciencia* (2011), 53:57-65

32.Prasad garrepalley, Sachin B somwanshi, Ramadas T Dolas, Vivekanand A Kashid, Kiran B Dhamak, Vinayak M Gaware, Atul N Khadse and Kiran B Kotade. A novel gastro retentive controlled release drug delivery system of Propanolol Hydrochloride: Formulation and evaluation. *J. Chem. Pharm. Research*, (2011), 3 (1) : 932-939.

33. *https://en.m.wikipedia.org>wiki>ezetimibe*

34.*www.drugs.com> Drugs A to Z*

35. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th Edition, RPS Publishers, Royal pharmaceutical society of Britain, 2009.

36.Varsha Balkrishna Mane, Surekha Babar, Nita Kulkarni. Development of UV Spectrophotometric method for the simultaneous estimation of Simvastatin and Ezetimibe in tablet dosage form by simultaneous equation and absorbance ratio method. *IJPR* (2011), 3(30, 1459-1466.

37. Rakesh Pawha, Lovely Chhabra, Avneet Kaur Lamba, Sumit Jindal, Arvind Rathour. Formulation and *In vitro* Evaluation of Effervescent Floating tablets of an Antiulcer Agent. *Journal of Chemical and Pharmaceutical Research*. (2012), 4(2), :1066-1073.

38. Allen, Loyd V Remington-*The science and practice of pharmacy.* 21Ed. Maryland, USA; Lipincott, Williams and Wilkins; 2005:720-730.

39. Lachman L. Lieberman H A, Kanig J L. *The theory and practice of Industrial Pharmacy.* 4Ed. New Delhi, India; Varghese publishing house; 1991:66-71.

40. Praveen Nasa, Sheefali Mahant, Deepika Sharma. Floating Systems: A Novel Approach Towards Gastroretentive Drug Delivery Systems. International Journal of Pharmacy and Pharmaceutical Sciences. (2010), 2(3): 2-7.

41. Sreekanth Babu, Ajay Kumar A, Suman DR, Parvathi M. Controlled release Effervescent Floating Matrix tablets of Moxifloxacin Hydrochloride: Development, Optimization and *In vitro* Evaluation. *International journal of Medicine and Pharmaceutical Research* (2013), 1(3), 286-293

42. Ravala JA, Patela JK, Lib N, Patela MM. Ranitidine hydrochloride floating matrix tablets based on low density powder: effects of formulation and processing parameters on drug release. *Asian Journal of Pharmaceutical Sciences.*2007;2(4): 130-142.

43. Praveen Kumar, Yusra Ahmad, Amitav Ghosh. A stability indicating RP-HPLC method development for determination of ezetimibe in tablet dosage form. *Der Pharma Chemica*, (2012), 4 (3):1296-1304.

44. R Kapil, Tsai YH, Yang WC, Chang JS, Wu PC,Takayama K. Once-daily Rivastigmine Gastro-retentive floating tablet dosage form:formulation design and *in vitro/in vivo* investigation. *Journal of drug delivery system*, (2012), 58:607-614.

45. Patel SS, Ray S, Thakur RS. Formulation and evaluation of floating drug delivery system containing clarithromycin for helicobacter pylori. *Acta Poloniae Pharmaceutica*-Drug Research. (2006); 63(1):53-61

46. Srikanth MV, Sreenivasa Rao N, Sunil SA, Sharma GS, Uhumwangho MU, Ramana Murthy KV. Formulation and evauation of gastro retentive floating drug delivery system of Ofloxacin. *Drug Invention Today,*(2011), 3(3):7-9.

47.ICH Q1A guidelines: Stability testing of existing drug and drug products. Available at : *http:// www.ichguidelines.com*

48.Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Control Release*. (2000); 63:235-59.

49. Higuchi T. Mechanism of sustained action medication: Theoritical analysis of rate of release of solid drug dispersed in solid matrices. *J Pharma Science.* (1963), 52:1145-1149.